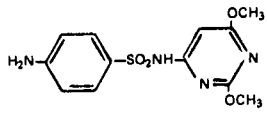
SULFADIMETHOXINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(2,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide

Common Name: Sulforthomidine; sulphormethoxine

Structural Formula:



Chemical Abstracts Registry No.: 122-11-2

Trade Name	Manufacturer	Country	Year Introduced
Madribon	Roche	U.S.	1958
Madrigid	Roche	U.S.	1959
Abcid	Daiichi	Japan	–
Albon	Roche	U.S.	–
Ancosul	Anchor	U.S.	–
Asthoxin	Kobayashi	Japan	–
Bensulfa	Caber	Italy	–
Chemiosalfa	Salfa	Italy	–
Crozinal	Borromeo	Italy	–
Deltin	Wassermann	Italy	–
Deposol	Pliva	Yugoslavia	–
Diasulfa	Crosara	Italy	–
Diazinol	Washington	Italy	–
Dimetossilina	Lister	Italy	–
Dimetossin	Caber	Italy	–
Dimetoxan	Nessa	Spain	–
Dimetoxin	Nissin	Japan	–
Dimexin	Fuso	Japan	–
Duramid	Deva	Turkey	–
Emerazina	Croce Bianca	Italy	–
Fultamid	Fulton	Italy	–
Hachimetoxin	Toyo	Japan	–
Ipersulfa	Ion	Italy	–
Jatsulph	Clinimed	S. Africa	–
Lensulpha	Lennon	S. Africa	–
Levisul	A.F.I.	Italy	–
Madribon	Roche	Italy	–
Madroxin	Polfa	Poland	–
Melfa	Tanabe	Japan	–
Micromega	Sidus	Italy	–
Mition D	Taisho	Japan	–
Neostreptal	Locatelli	Italy	–
Neosulfamyd	Libra	Italy	–
Omnibon	Yamanouchi	Japan	–
Oxazina	Made	Spain	–
Redifal	A.M.S.A.	Italy	–
Risulpir	Lisapharma	Italy	–
Ritarsulfa	Benvegna	Italy	–
Scandisil	Firma	Italy	–
Sulfabon	Vaillant	Italy	–
Sulfadomus	Medici Domus	Italy	–

Trade Name	Manufacturer	Country	Year Introduced
Sulfaduran	Janus	Italy	–
Sulfalon	Sumitomo	Japan	–
Sulfastop	Vis	Italy	–
Sulfathox	SCS Pharmalab	S. Africa	–
Sulfoplan	Gea	Denmark	–
Sulf-Reten	Pons	Spain	–
Sulmethon	Mohan	Japan	–
Sulmetoxyn	Nichiiku	Japan	–
Sulxin	Chugai	Japan	–
Sumetamin	Samva	Japan	–
Tempodiazina	C.I.F.	Italy	–

Raw Materials

Sodium sulfanilamide
4-Phenylsulfonyl-2,6-dimethoxypyrimidine

Manufacturing Process

1.4 g of 4-phenylsulfonyl-2,6-dimethoxypyrimidine and 4 g of sodium sulfanilamide (both dried over potassium hydroxide) were very finely ground and heated in an oil bath for 10 hours at 120°C (inside temperature). The reaction mixture was taken up in 30 ml of water and treated with 3 ml of 2 N sodium hydroxide solution. After standing for one hour at 0°C, the turbid solution was filtered and the filtrate was made alkaline with sodium carbonate. After again standing for one hour at 0°C, the precipitate was filtered off (1.9 g of regenerated sulfanilamide) and the filtrate was neutralized with acetic acid, whereupon crystallization resulted. The isolated crystals of 4-sulfanilamido-2,6-dimethoxypyrimidine weighed 1.3 g (84% of theory), melting point 190°C to 196°C.

References

Merck Index 8775
Kleeman & Engel p. 835
OCDS Vol. 1 pp. 125, 129 (1977)
I.N. p. 899
Bretschneider, H. and Klotzer, W.; U.S. Patent 2,703,800; March 8, 1955; assigned to Oesterreichische Stickstoffwerke AG
Bretschneider, H. and Klotzer, W.; U.S. Patent 3,127,398; March 31, 1964; assigned to Hoffmann-LaRoche, Inc.

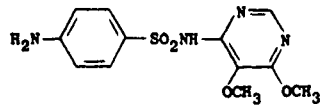
SULFADOXINE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-(5,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide

Common Name: Sulforthomidine; sulformethoxine

Structural Formula:



Chemical Abstracts Registry No.: 2447-57-6

Trade Name	Manufacturer	Country	Year Introduced
Fanasil	Roche	Italy	1973
Fansidar	Roche	U.S.	1982

Raw Materials

α-Methoxycyanoacetic acid methyl ester
Thiourea
Sodium
Methanol
Methyl iodide
Phenyltrimethylammonium toluene sulfonate
p-Acetylaminobenzenesulfonyl chloride

Manufacturing Process

(a) α-methoxy-cyanoacetic acid methyl ester is condensed with thiourea, in the presence of sodium methylate, to form 2-thio-4-amino-5-methoxy-6-hydroxy-pyrimidine.

(b) The product thus obtained is methylated in a sodium methylate solution with methyl iodide to form 2-methylthio-4-amino-5-methoxy-6-hydroxy-pyrimidine of MP 203°C, from water.

(c) The latter product is methylated with phenyltrimethylammonium-toluenesulfonate to form 2-methylthio-4-amino-5,6-dimethoxy-pyrimidine of MP 112° to 115°C, from 20% methanol.

(d) 0.9 gram of 2-methylthio-4-amino-5,6-dimethoxy-pyrimidine are dissolved in 3 ml of absolute pyridine. At 0°C, 1.2 grams of p-acetylaminobenzenesulfonyl chloride are added thereto and the mixture is shaken until all the material is dissolved. The solution is allowed to stand for 22 hours at 0°C and the pyridine eliminated in vacuo at 20°C. To the resulting product are added 20 ml of water and 3 ml of glacial acetic acid, whereupon the whole mixture is heated to the boil, thus causing crystallization. The crude product obtained is dissolved in 40 ml of 2.5% soda solution, and the solution obtained is filtered and supersaturated with gaseous carbon dioxide. There is thus obtained 1.5 grams (85%) of 2-methylthio-4-(N_4-acetyl-sulfanilamido)-5,6-dimethoxy-pyrimidine of MP 220° to 221°C, from 50% ethanol.

(e) 1.3 grams of 2-methylthio-4-(N_4-acetyl-sulfanilamido)-5,6-dimethoxy-pyrimidine are dissolved in 25 ml of water and 0.4 gram of anhydrous sodium carbonate, then refluxed for 3½ hours in the presence of 6 to 7 grams of Raney nickel. Then, a solution of 1 gram of sodium hydroxide in 3 ml of water is added thereto and heating continued for another hour. The catalyst is filtered off and the filtrate acidified to Congo red with hydrochloric acid. The pH is then brought to 5 by means of ammonia, thus causing crystallization. There is thus obtained 0.51 gram of 4-sulfanilamido-5,6-dimethoxy-pyrimidine of MP 190° to 194°C, from 50% ethanol.

References

Merck Index 8776
PDR p. 1484
I.N. p. 899
REM p. 1176
Bretschneider, H., Klotzer, W. and Schantl, J.; U.S. Patent 3,132,139; May 5, 1964; assigned to Hoffmann-La Roche Inc.

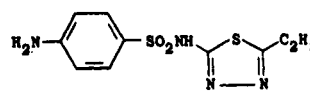
SULFAETHIDOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 94-19-9

Trade Name	Manufacturer	Country	Year Introduced
Sul-Spansion	SKF	U.S.	1956
Globucid	Schering	–	–
Spasmo-Urosulf	T.A.D.	W. Germany	–
Sulfa-Perlongit	Boehr. Ing.	W. Germany	–
Urosulf	T.A.D.	W. Germany	–

Raw Materials

2-Amino-5-ethyl-1,3,4-thiadiazole
p-Acetylaminobenzene sulfonyl chloride

Manufacturing Process

0.163 mol of 2-amino-5-ethyl-1,3,4-thiadiazole was covered with 43 parts of anhydrous pyridine. To the mixture was added 50 parts (0.214 mol) of p-acetylaminobenzene sulfonyl chloride with vigorous shaking at 50°C to 60°C. The reaction mixture was then heated to 125°C. When the mixture had cooled somewhat it was placed in a Claisen flask and 27.6 parts (0.69 mol) of sodium hydroxide dissolved in 110 parts of water was added through a dropping funnel while distilling off a mixture of pyridine and water. The distillation was stopped when the temperature reached 100°C and the residual liquor in the flask heated at 95°C for 30 minutes.

The reaction mixture was then poured into 1,650 parts of hot water, the pH adjusted to 8 to 9, decolorizing charcoal was added and the whole was heated on the steam for 15 minutes. The charcoal was filtered off and the hot filtrate neutralized and cooled. The 2-(sulfanilamido)-5-ethyl-1,3,4-thiadiazole was purified by repeated crystallization from boiling water.

References

Merck Index 8777
Kleeman & Engel p. 836
OCDS Vol. 1 p. 125 (1977)
I.N. p. 900
Roblin, R.O. Jr. and Winner, P.S.; U.S. Patent 2,358,031; September 12, 1944; assigned to American Cyanamid Co.

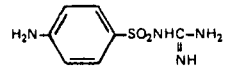
SULFAGUANIDINE

Therapeutic Function: Antimicrobial

Chemical Name: 4-Amino-N-(aminoiminomethyl)benzenesulfonamide

Common Name: Sulfanilylguanidine

Structural Formula:



Chemical Abstracts Registry No.: 57-67-0

Trade Name	Manufacturer	Country	Year Introduced
Sulfaguanidine	Lederle	U.S.	1941
Aseptil-Guanadina	Wassermann	Italy	–
Aterian	Takeda	Japan	–
Devaguanil	Deva	Turkey	–
Ganidan	Specia	France	–
Guabeta	O.T.W.	W. Germany	–
Guasept	Ferrosan	Denmark	–
Resulfon	Nordmark	W. Germany	–

Raw Materials

Guanidine hydrochloride
p-Nitrobenzene sulfonyl chloride
Iron
Hydrogen chloride

Manufacturing Process

10 parts of guanidine hydrochloride (0.1 mol) was dissolved in 75 parts of water and the pH adjusted to 8 to 9. The solution was warmed to 50°C to 60°C and kept at this temperature while a slurry of 25 parts (0.113 mol) of p-nitrobenzene sulfonyl chloride was added slowly with mechanical stirring. The pH was kept at 8 to 9 by the addition of 40% sodium hydroxide solution. At the end of the reaction the solution was cooled and filtered from the separated solid. The p-nitrobenzene sulfonyl guanidine was recrystallized from hot water.

5 parts (0.024 mol) of p-nitrobenzene sulfonyl guanidine was dissolved in 50 parts of boiling 95% alcohol and to the solution was added 0.5 part of concentrated hydrochloric acid. The solution was heated to reflux and 6 parts of iron dust was added. The suspension was refluxed for 3 hours, made basic with potassium carbonate, and filtered hot. The alcohol was evaporated off and the p-aminobenzene sulfonyl guanidine recrystallized from boiling water with the addition of decolorizing charcoal.

References

Merck Index 8779
Kleeman & Engel p. 837
OCDS Vol. 1 p. 123 (1977)
I.N. p. 900
Winnek, P.S.; U.S. Patent 2,218,490; October 15, 1940; assigned to American Cyanamid Co.
Winnek, P.S.; U.S. Patent 2,229,784; January 28, 1941; assigned to American Cyanamid Co.
Winnek, P.S.; U.S. Patent 2,233,569; March 4, 1941; assigned to American Cyanamid Co.

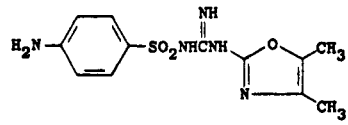
SULFAGUANOL

Therapeutic Function: Antibacterial

Chemical Name: N^1-[(4,5-dimethyl-2-oxazolyl)amidino] sulfanilamide

Common Name: Sulfadimethyloxazolylguanidine

Structural Formula:



Chemical Abstracts Registry No.: 27031-08-9

Trade Name	Manufacturer	Country	Year Introduced
Enterocura	Nordmark	W. Germany	1973
Enterocura	De Angeli	Italy	1981

Raw Materials

N^1-[p-Aminobenzenesulfonyl]-N^3-cyanoguanidine
Acetoin
Hydrogen chloride

Manufacturing Process

23.9 grams (0.1 mol) of N^1-[p-amino benzene sulfonyl]-N^3-cyano guanidine and 13.2 grams (0.15 mol) of acetoin are thoroughly stirred in a mixture of 120 cc of water and 120 cc of methanol. 25 cc of concentrated hydrochloric acid are added dropwise with stirring to this suspension at 40°C. A clear solution is obtained after 30 minutes which solution is kept at 40°C for another hour. Thereafter, the methanol is distilled off in a vacuum, the remaining solution is treated with charcoal and the pH of the filtered solution is quickly brought to 11 by addition of 10% soda lye with quick stirring.

The compound at first precipitated is redissolved at a pH of 11. The solution is treated another time with charcoal and is filtered. Thereafter, a mixture of anhydrous acetic acid and water in a proportion of 1:1 is added with stirring and cooling until a pH of 7 is reached. Thus, the reaction product separates with crystallization.

For purification, the product is recrystallized from 15 times the amount of a 9:1 mixture of acetone and water. The resulting N^1-[p-amino benzene sulfonyl]-N^3-(4,5-dimethyl-oxazolyl-(2)] guanidine is obtained as colorless crystals having a MP of 233° to 236°C.

References

Merck Index 8780
Kleeman & Engel p. 838
DOT 9 (5) 185 (1973)
I.N. p. 900
Loop, W., Baganz, H., Kohlmann, F.-W. and Schultze, H.; U.S. Patent 3,562,258; Feb. 9, 1971; assigned to Nordmark-Werke GmbH, Germany

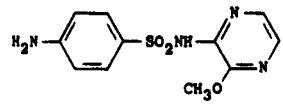
SULFALENE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-(3-methoxypyrazinyl)benzenesulfonamide

Common Name: Sulfamethopyrazine

Structural Formula:



Chemical Abstracts Registry No.: 152-47-6

Trade Name	Manufacturer	Country	Year Introduced
Longum	Farmitalia	W. Germany	1962
Kelfizina	Farmitalia	Italy	1962
Kelfizine	Farmitalia	U.K.	1969
Kelfizine	Bellon	France	1969

Raw Materials

2-Aminopyrazine
Sodium
p-Acetylaminobenzene sulfonyl chloride
Hydrogen
Bromine
Methanol
Sodium hydroxide

Manufacturing Process

2-Amino-3,5-Dibromo-Pyrazine: 112.7 ml of bromine in 375 ml of acetic acid are slowly added at 0° to +2°C, while stirring, to a solution of 95.11 grams of 2-amino-pyrazine and 326.5 grams of acetic acid trihydrate ($CH_3COONa \cdot 3H_2O$) in 1,480 ml of acetic acid. This addition requires about 2 to 3 hours and it is carried out in the dark. The mixture is then allowed to stand at room temperature (25° to 30°C) for 15 to 16 hours. About 1.5 liters of acetic acid are distilled off under vacuum (12 to 14 mm Hg) at 35°C and the brown and viscous residue is poured into 500 grams of ice-water under stirring.

Aqueous 20% sodium hydroxide is added in order to obtain a pH = 8 and then the product is filtered and air-dried. The air-dried product is extracted 6 times with 150 ml of ether; the filtered ethereal solutions are evaporated to dryness and the residue (50 to 52 grams) is crystallized from hot water. The yield is 34.36 grams, melting at 114°C.

2-Amino-3-Methoxy-5-Bromo-Pyrazine: 7 grams of 2-amino-3,5-dibromo-pyrazine are boiled for 9 hours in a methanolic solution of sodium methylate (obtained from 0.65 gram of Na and 18.5 ml of methanol). By cooling a crystalline product is obtained, filtered and washed once with methanol and 2 to 3 times with water. The yield is 5.4 grams, melting at 138°C.

2-Amino-3-Methoxy-Pyrazine: 3 grams of 2-amino-3-methoxy-5-bromo-pyrazine are hydrogenated, in methanolic solution at room temperature and at atmospheric pressure, in the presence of 1 gram of palladium over charcoal (10%) and 0.9 gram of potassium hydroxide. When the stoichiometric amount of hydrogen is absorbed, the suspension is filtered and the filtrate is evaporated to dryness. The residue is extracted with acetone, the acetonic solution is evaporated and the residue (1.8 grams, melting at 75° to 82°C) is crystallized from cyclohexane. The yield is 1.5 grams, melting at 85°C.

2-(p-Acetylaminobenzene-sulfonamido)-3-Methoxy-Pyrazine: 1.5 grams of 2-amino-3-methoxy-pyrazine dissolved in 15 ml of anhydrous pyridine are treated, under cooling and stirring, with 2.81 grams of p-acetylaminobenzene-sulfonyl-chloride, at small portions in about 30 minutes. The mixture is allowed to stand for 20 hours at room temperature and then is heated to 50°C for 4 hours.

The solution is concentrated to one-third of its volume, under vacuum, and poured into ice-water under stirring. The precipitate is filtered and washed with water. 2.21 grams melting at 218° to 220°C are obtained. The MP (crystallized from alcohol) is 224°C.

2-Sulfanilamido-3-Methoxy-Pyrazine: 1.5 grams of the product from the preceding step and 7 to 8 ml of aqueous 10% sodium hydroxide are boiled for 1 hour. The cooled solution is slightly acidified to pH 6 with aqueous 2 N hydrochloric acid and the product is filtered. The yield is 1.25 grams, melting at 175°C.

References

Merck Index 8781
Kleeman & Engel p. 838
OCDS Vol. 1 p. 125 (1977)
I.N. p. 901
Camerino, B. and Palamidessi, G.; U.S. Patent 3,098,069; July 16, 1963; assigned to Societa Farmaceutici Italia, Italy

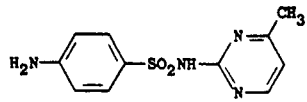
SULFAMERAZINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(4-methyl-2-pyrimidinyl)benzenesulfonamide

Common Name: Sulfamethyldiazine; methylsulfadiazine

Structural Formula:



Chemical Abstracts Registry No.: 127-79-7

Trade Name	Manufacturer	Country	Year Introduced
Sulfamerazine	Lederle	U.S.	1943
Dosulfin	Geigy	W. Germany	–
Mebacid	Veb Berlin Chemie	E. Germany	–
Polagin	De Angeli	Italy	–
Percoccide	A.C.F.	Neth.	–
Romezin	Tanabe	Japan	–
Septosil	Egyt	Hungary	–
Solumedine	Specia	France	–
Spanbolet	Norden	U.S.	–

Raw Materials

2-Amino-6-methyl pyrimidine
p-Acetylaminobenzene sulfonyl chloride
Hydrogen chloride

Manufacturing Process

To a well agitated solution of 6.95 grams of 2-amino-6-methyl pyrimidine in 40 cc of pyridine, 15 grams of p-acetylaminobenzenesulfonyl chloride are added in small portions over a 30 minute period. The reaction mixture is then heated on a steam bath for 30 minutes, the free pyridine being then removed under reduced pressure and the residue mixed with cold water, and the latter mixture is vigorously stirred. The solid reaction product is removed by filtration and washed with cold water.

There is obtained a yield of 14 grams of crude 2-(p-acetylaminobenzenesulfonamido)-6-methyl pyrimidine, which on recrystallization from alcohol and water melts at 238° to 239°C. The crude product is hydrolyzed by suspending it in 400 cc of 2 N hydrochloric acid and warming until solution is complete. The solution is neutralized with sodium carbonate and the precipitated 2(sulfanilamido)-6-methyl pyrimidine is removed by filtration. The latter on recrystallization from alcohol and water shows a melting point of 225° to 226°C.

References

Merck Index 8783
Kleeman & Engel p. 839
OCDS Vol. 1 pp. 124, 128 (1977)
I.N. p. 901
REM p. 1173
Sprague, J.M.; U.S. Patent 2,407,966; September 17, 1946; assigned to Sharp & Dohme, Inc.

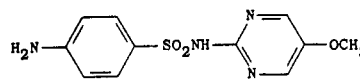
SULFAMETER

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(5-methoxy-2-pyrimidinyl)benzenesulfonamide

Common Name: Sulfamethoxydiazine

Structural Formula:



Chemical Abstracts Registry No.: 651-06-9

Trade Name	Manufacturer	Country	Year Introduced
Sulla	Robins	U.S.	1968
Bayrena	Bayer Pharma	France	–
Durenat	Bayer/Schering	W. Germany	–
Durenate	Bayer	U.K.	–
Fortesul	Pliva	Yugoslavia	–
Kirocid	Schering	W. Germany	–
Kiron	Schering	W. Germany	–
Ultrax	Chemie Linz.	Austria	–

Raw Materials

Methoxymalonic acid ester
Phosphorus oxychloride
Carbethoxy-sulfanilic acid chloride
Guanidine carbonate
Zinc
Sodium hydroxide

Manufacturing Process

2-Amino-5-methoxy pyrimidine is obtained having a melting point of about 300°C by condensation of methoxymalonic acid ester with guanidine carbonate in the presence of sodium ethylate. The resultant reaction product is then converted to 2-amino-5-methoxy-4,6-dichloropyrimidine (melting point 216°C to 217°C) by heating this reaction product with phosphorus oxychloride. The dichloro compound is then suspended in water with zinc dust and

is tested in the presence of caustic alkaline or carbonates to produce the 2-amino-5-methoxy pyrimidine compound, melting point 80°C to 82°C, (benzene).

12.6 g of 2-amino-5-methoxy pyrimidine, 26.4 g of carbethoxy-sulfanilic acid chloride and 50 cc of dry pyridine are heated for 30 minutes with frequent shaking to a temperature of 80°C. The reaction product is then mixed with 200 cc of water and with dilute hydrochloric acid (0.1 N) until the reaction is acid to Congo Red indicator. A precipitate is formed which is then filtered under suction, washed with distilled water, and dried at 150°C. A practically quantitative yield is recovered of 2-(p-carbethoxyaminobenzene-sulfonamido)-5-methoxy-pyrimidine, melting point 248°C to 250°C.

To hydrolyze the sulfa pyrimidine compound, the same is heated at 90°C with 200 cc of 2N potassium hydroxide solution for about one hour until complete solution is obtained. The resultant solution is then cooled to room temperature (25°C) and acidified with acetic acid to precipitate the hydrolyzed product, which is then recrystallized from dilute acetone admixed with animal charcoal.

References

Merck Index 8785
Kleeman & Engel p. 841
OCDS Vol. 1 pp. 125, 129 (1977)
I.N. p. 902
Diedrich, P.; U.S. Patent 3,214,335; October 26, 1965; assigned to Schering A.G. (Germany)

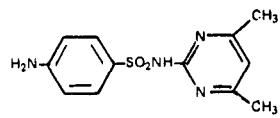
SULFAMETHAZINE

Therapeutic Function: Antimicrobial

Chemical Name: 4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide

Common Name: Sulfamezathine, sulfadimerazine, sulfamidine, sulfadimethylpyrimidine, sulfadimidine (U.K. Name)

Structural Formula:



Chemical Abstracts Registry No.: 57-68-1

Trade Name	Manufacturer	Country	Year Introduced
Cremomethazine	MSD	U.S.	1947
Deladine	Delmaak	S. Africa	—
Intradine	Norbrook	U.K.	—
Rigesol	Ferrosan	Denmark	—
Rivodine	Rivopharm	Switz.	—
S-Dimidine	Protea	Australia	—
Sulphix	Protina	W. Germany	—

Raw Materials

p-Aminobenzenesulfonamidoguanidine
Sodium acetylacetonate

Manufacturing Process

A flask heated in an oil bath is filled with 600 ml water and 60 g (1 mol) glacial acetic acid (or an equivalent quantity of diluted acetic acid). While stirring 235 g (1.1 mols) anhydrous p-aminobenzenesulfonamidoguanidine (or an equivalent quantity of a nonanhydrous product) and 122 g (1 mol) sodium acetylacetonate 100% purity (or an equivalent quantity of product of a lower purity) are introduced into the flask while stirring.

The temperature of the reaction mixture is brought to 102°C to 103°C, the mixture is further stirred at this temperature during 24 hours. The pH value of the mixture, which should range between 5 and 6 is checked during the reaction.

On expiry of the reaction period heating is cut off, the mass being cooled or allowed to cool down to 60°C.

Filtering under suction is effected, the solids on the filter being washed with 100 ml water at 80°C.

After drying of the product on the filter 256 g of 2-p-aminobenzenesulfonamido-4,6-dimethylpyrimidine, melting point 196°C to 197°C, purity 99.5% are obtained. The output is 92% of the theory calculated with respect to the sodium acetylacetonate employed.

References

Merck Index 8786
I.N. p. 839
REM p. 1173
Sprague, J.M.; U.S. Patent 2,407,966; September 17, 1946; assigned to Sharp & Dohme, Inc.
Garzia, A.; U.S. Patent 3,119,818; January 28, 1964; assigned to Istituto Chemioterapico Italiano SpA

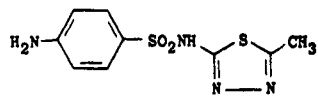
SULFAMETHIZOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-(5-methyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide

Common Name: Sulfamethylthiadiazole

Structural Formula:



Chemical Abstracts Registry No.: 144-82-1

Trade Name	Manufacturer	Country	Year Introduced
Thiosulfil	Ayerst	U.S.	1953
Sulfurine	Table Rock	U.S.	1963
Ultrasul	Webcon	U.S.	1963
Sulfasol	Hyrex-Key	U.S.	1963
Renasul	Century	U.S.	1966
Famet	Calmic	Australia	–
Harnway	Nichiiko	Japan	–
Rufol	Debat	France	–

Trade Name	Manufacturer	Country	Year Introduced
Salimol	Maruishi	Japan	–
S-Methizole	Protea	Australia	–
Starisil	Star	Finland	–
Sulfa Gram	Beach	U.S.	–
Sulfametin	Pharmacia	Sweden	–
Urobiotic	Roerig	U.S.	–
Urokinon	Chugai	Japan	–
Urokizol	Chugai	Japan	–
Urolex	Ohio Medical	U.S.	–
Urosol	Kanto	Japan	–
Urosul	Mohan	Japan	–
Utrasul	Chicago Pharmacal	U.S.	–

Raw Materials

Acetaldehyde thiosemicarbazone
p-Acetaminobenzolsulfonyl chloride
Calcium ferricyanide

Manufacturing Process

To 10 grams acetaldehyde-thiosemicarbazone in 80 grams pyridine gradually 20 grams p-acetaminobenzolsulfonylchloride is added. The reaction mixture is heated about 1 hour on a water bath and is then charged in 1 liter water, to which some acetic acid is added. The bottom sediment is sucked off and washed with water, after which it is crystallized by alcohol. 20 grams of the condensation product thus obtained is cleared in 100 cc water at about 30°C, after which 45 grams calcium ferricyanide dissolved in about 100 cc water is added. The reaction mixture is made slightly alkaline and held at a temperature of about 80°C for 2 to 3 hours. It is important that the reaction mixture during the whole period of 2 to 3 hours is steadily held alkaline.

After the said 2 to 3 hours the liquid is cooled and the bottom sediment, which has a greenish color, is filtered off. The liquid sucked off eventually is treated with active carbon, filtered and made slightly acid by means of acetic acid, at which 2-amino-benzolsulfonamido-5-methyl-1,3,4-thiodiazol (melting point 204° to 206°C) is precipitated.

References

Merck Index 8787
Kleeman & Engel p. 839
PDR pp. 650, 1533
OCDS Vol. 1 p. 125 (1977)
I.N. p. 901
REM p. 1174
Hübner, O.; U.S. Patent 2,447,702; August 24, 1948; assigned to H. Lundbeck & Co., Kemisk Pharmaceutisk Laboratorium A/S, Denmark

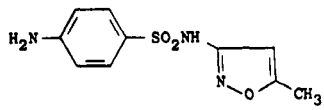
SULFAMETHOXAZOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-(5-methyl-3-isoxazolyl)benzenesulfonamide

Common Name: Sulfisomezole

Structural Formula:



Chemical Abstracts Registry No.: 723-46-6

Trade Name	Manufacturer	Country	Year Introduced
Gantanol	Roche	U.S.	1961
Urobax	Shionogi	U.S.	1980
Azo Gantanol	Roche	U.S.	–
Bactrim	Roche	U.S.	–
Comoxol	Squibb	U.S.	–
Cotrim	Lemmon	U.S.	–
Gantaprim	Ausonia	Italy	–
Metoxal	Farmos	Finland	–
Septra	Burroughs Wellcome	U.S.	–
Sinomin	Shionogi	Japan	–
Sulfatrim	Schein	U.S.	–
Urobak	Shionogi	Japan	–

Raw Materials

Ethyl 5-methylisoxazole-3-carbamate
Sodium hydroxide
Acetylsulfanil chloride

Manufacturing Process

Preparation of 3-Amino-5-Methylisoxazole: 1.7 grams of ethyl 5-methylisoxazole-3-carbamate was heated on a boiling water-bath with 5 cc of a 10% aqueous sodium hydroxide solution for 8 hours, then the reaction mixture was extracted several times with ether or benzene and the extract was cooled followed by the removal of the solvent and drying. The residue was solidified after a while and gave prismatic crystals, melting point 61° to 62°C, of 3-amino-5-methylisoxazole by recrystallization from benzene.

Preparation of 3-Acetylsulfanilamido-5-Methylisoxazole: 0.9 gram of 3-amino-5-methylisoxazole in 5 cc of pyridine was allowed to react with 2.0 grams of acetylsulfanil chloride accompanied by the generation of heat. After about one hour, water was added to the reaction mixture and the crystal precipitated out was recrystallized from alcohol to give 2.5 grams of 3-acetylsulfanilamido-5-methylisoxazole, melting point (decomposition) 220° to 221°C.

Preparation of 3-Sulfanilamido-5-Methylisoxazole: 2 grams of 3-acetylsulfanilamido-5-methylisoxazole was heated with 10 cc of an aqueous sodium hydroxide solution on a water-bath for one hour and after cooling the reactant was acidified by addition of acetic acid. The precipitate thus formed was recrystallized from dilute alcohol to give 15 grams of colorless prisms of 3-sulfanilamido-5-methylisoxazole, melting point 167°C.

References

Merck Index 8789
Kleeman & Engel p. 840
PDR pp. 673, 763, 830, 993, 1034, 1473, 1606, 1738
DOT 7 (5) 189 (1971)
I.N. p. 901
REM p. 1174
Kano, H., Nishimura, H., Nakajima, K. and Ogata, K.; U.S. Patent 2,888,455; May 26, 1959; assigned to Shionogi & Co., Ltd., Japan

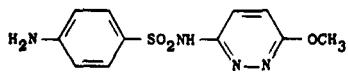
SULFAMETHOXYPYRIDAZINE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-(6-methoxy-3-pyridazinyl)benzenesulfonamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 80-35-3

Trade Name	Manufacturer	Country	Year Introduced
Kynex	Lederle	U.S.	1957
Midicel	Parke Davis	U.S.	1957
Aseptilex	Wassermann	Spain	–
Asey-Sulfa	Quimia	Spain	–
B-Sulfamethoxy	Biokema	Switz.	–
Davosin	Parke Davis	W. Germany	–
Durasul	Estedi	Spain	–
Exazol	Andreu	Spain	–
Fercasulf	Arco	Switz.	–
Lederkyn	Lederle	U.K.	–
Lentosulfa	I.S.F.	Italy	–
Longamid	A.L.	Norway	–
Longisul Jarabe	Landerlan	Spain	–
Metazina	Piam	Italy	–
Microcid	Borromeo	Italy	–
Novosulfin	Galenika	Yugoslavia	–
Oroxin	Otsuka	Japan	–
Paramid Supra	Kwizda	Austria	–
Pirasulfon	Neo	Canada	–
S.D.M.	Barlow Cote	Canada	–
Sulfabon	Biokema	Switz.	–
Sulamin	Pliva	Yugoslavia	–
Sulfadazina	Guidi	Italy	–
Sulfadepot	Almirall	Spain	–
Sulfadin	C.I.F.	Italy	–
Sulfaintensa	Robert	Spain	–
Sulfalex	De Angeli	Italy	–
Sulfamizina	Wells	Italy	–
Sulfamyd	Libra	Italy	–
Sulfapyrazin	Bosnalijek	Yugoslavia	–
Sulfatar	Arnaldi	Italy	–
Sulfocidan	Cidan	Spain	–
Sulforetent	Cifa	Italy	–
Sulfo-Rit	Aristochimica	Italy	–
Sultirene	Specia	France	–
Unisulfa	Angelini	Italy	–

Raw Materials

3-Sulfanilamido-6-chloropyridazine
Sodium
Methanol

Manufacturing Process

The following description is taken from U.S. Patent 2,712,012: 2.3 parts of clean sodium metal is dissolved in 50 parts of anhydrous methyl alcohol. 11.4 parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture heated in a sealed tube 13 hours at 130° to 140°C. After the tube has cooled it is opened and the reaction mixture filtered, acidified with dilute acetic acid, then evaporated to dryness on the steam bath. The residue is dissolved in 80 parts of 5% sodium hydroxide, chilled and acidified with dilute acetic acid. The crude product is filtered and then recrystallized from water to give 3-sulfanilamido-6-methoxypyridazine of melting point 182° to 183°C.

References

Merck Index 8790
Kleeman & Engel p. 842
OCDS Vol. 1 pp. 124, 131 (1977)
I.N. p. 902
Clark, J.H.; U.S. Patent 2,712,012; June 28, 1956; assigned to American Cyanamid Co.
Murphy, D.M. and Shepherd, R.G.; U.S. Patent 2,833,761; May 6, 1958; assigned to American Cyanamid Co.

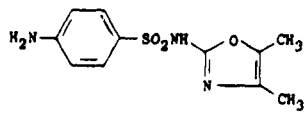
SULFAMOXOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(4,5-dimethyl-2-oxazolyl)benzenesulfonamide

Common Name: Sulfadimethyloxazole

Structural Formula:



Chemical Abstracts Registry No.: 729-99-7

Trade Name	Manufacturer	Country	Year Introduced
Sulfuno	Nordmark	W. Germany	1960
Justamil	Anphar-Rolland	France	1961
Justamil	Anphar-Rolland	Italy	1964
Naprin	Upjohn	U.S.	–
Oxasulfa	Trinum	Italy	–
Tardamide	Gruenenthal	W. Germany	–

Raw Materials

2-Amino-4,5-dimethyloxazole
p-Acetaminobenzenesulfonyl chloride
Hydrogen chloride

Manufacturing Process

11.2 g of 2-amino-4,5-dimethyloxazole (0.1 mol), 46.8 g of anhydrous p-acetaminobenzenesulfonyl chloride (0.2 mol) and 60 cc of methylene chloride are mixed and then treated while stirring and with exclusion of water with 12.0 g (0.2 mol) of anhydrous trimethylamine, dis-

solved in 60 cc of benzene. After adding the trimethylamine, the mixture is heated for 30 minutes to 40°C, left to stand for 12 hours and then the solvent is distilled off. The distillation residue is heated with 300 cc of water until the residual organic solvents are driven off. The residue is filtered and thoroughly washed with water. Yield of condensation product: 46.4 g. The mass is triturated with 80 cc of cold 2.5% caustic soda solution, filtered and thoroughly washed with water. The residue which is insoluble in caustic soda solution consists of bis-(p-acetaminobenzenesulfonyl)-2-amino-4,5-dimethyloxazole. It melts indefinitely between 201°C and 206°C with decomposition (browning). Yield: 42.3 g corresponding to 83.6%.

The 42.3 g of the bis-compound are heated under reflux in 210 cc of 96% ethanol containing 10% of hydrogen chloride, to the boiling point of the alcohol. After dissolution, the substance is boiled for 20 minutes under reflux. It is cooled, filtered and washed with alcohol. By concentrating the mother liquor and the washing liquid by evaporation, further amounts of substance are obtained.

The total amount of the hydrochloride obtained is stirred with 50 cc of water and the mixture is mixed with 15 cc of 45% caustic soda solution. After complete dissolution, the mixture is treated with decolorizing carbon and the filtrate is brought to a pH value of 5.5 by means of hydrochloric acid. 17.6 g of p-aminobenzenesulfonyl-2-amino-4,5-dimethyloxazole are obtained as colorless crystals with a melting point of 193°C to 194°C (corrected), corresponding to a yield of 65.9% calculated on the basis of the 2-amino-4,5-dimethyloxazole used.

References

Merck Index 8797
Kleeman & Engel p. 843
OCDS Vol. 1 p. 124 (1977)
DOT 12 (9) 377 (1976)
I.N. p. 903
Loop, W., Luhrs, E. and Hauschildt, P.; U.S. Patent 2,809,966; October 15, 1957; assigned to Nordmark-Werke G.m.b.H. (Germany)

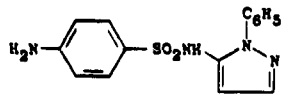
SULFAPHENAZOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 526-08-9

Trade Name	Manufacturer	Country	Year Introduced
Sulfabid	Purdue Frederick	U.S.	1962
Fenazolo	S.A.M.	Italy	–
Merian	Dainippon	Japan	–
Microsulf	Novafarnova	Italy	–
Orisul	Ciba	W. Germany	–

Trade Name	Manufacturer	Country	Year Introduced
Orisulf	Ciba	U.K.	–
Plisulfan	Pliva	Yugoslavia	–
Sulfapadil	Padil	Italy	–
Sulfazol	Barlocco	Italy	–
Sulfenal	Kanto	Japan	–
Sulforal	Farber-R.E.F.	Italy	–
Sulfostat	Bieffe	Italy	–
Sulphena	Nisshin	Japan	–

Raw Materials

3-Amino-2-phenylpyrazole
p-Carbethoxyaminobenzenesulfonyl chloride
Sodium hydroxide

Manufacturing Process

Into a solution of 15.9 grams of 3-amino-2-phenyl-pyrazole in 60 cc of anhydrous pyridine, 29 grams of p-carbethoxyamino-benzene sulfonyl chloride are introduced within about 25 minutes. When the reaction subsides, heating is carried out for a further hour to 90° to 95°C internal temperature. The reaction solution is then poured into 300 cc of 2 N hydrochloric acid. The precipitate is filtered with suction and recrystallized from dilute alcohol. The 3-(p-carbethoxyaminobenzene sulfonamido)-2-phenyl-pyrazole is obtained thus in white crystals of MP 175° to 176°C.

These are taken up in 250 cc of 2 N caustic soda solution and heated for 1 hour on a boiling water bath. With hydrochloric acid, the pH is then adjusted to 6 to 7 and the precipitate is filtered with suction and crystallized from 75% ethyl alcohol. The resulting 3-(p-aminobenzene sulfonamido)-2-phenyl-pyrazole crystallizes in white crystals and has a melting point of 177° to 178°C.

References

Merck Index 8810
Kleeman & Engel p. 844
OCDS Vol. 1 p. 124 (1977)
I.N. p. 904
Druey, J. and Schmidt, P.; U.S. Patent 2,858,309; October 28, 1958; assigned to Ciba Pharmaceutical Products Inc.

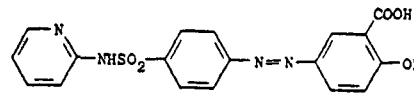
SULFASALAZINE

Therapeutic Function: Antibacterial

Chemical Name: 2-Hydroxy-5-[[4-[(2-pyridinylamino)sulfonyl] phenyl] azo] -benzoic acid

Common Name: Salicylazosulfapyridine, salazosulfapyridine

Structural Formula:



Chemical Abstracts Registry No.: 599-79-1

Trade Name	Manufacturer	Country	Year Introduced
Azulfidine	Pharmacia	U.S.	1952
Salazopyrine	Pharmacia	France	1958
Salazopyrin	Pharmacia	U.K.	1968
Salazopyrin	Green Cross	Japan	1969
S.A.S.-500	Rowell	U.S.	1972
Sulcolon	Lederle	U.S.	1974
Rorasul	Rorer	U.S.	1975
Colo-Pleon	Henning	W. Germany	–
Salisulf	Giuliani	Italy	–

Raw Materials

α-(p-Aminobenzenesulfonamido)pyridine
Sodium nitrite
Hydrogen chloride
Salicylic acid

Manufacturing Process

50 g of α-(p-aminobenzenesulfonylamido)pyridine are dissolved in a mixture of 50 cc of concentrated hydrochloric acid and 25 cc of water and diazotized with a solution of 13.8 g sodium nitrite. In the meantime 28 g of salicylic acid, 24 g of potassium hydroxide and 12 g of sodium carbonate are dissolved in water. The diazo suspension is added in portions to the alkaline solution of salicylic acid and the alkalinity maintained at a sufficiently high level during the whole reaction by means of addition of further quantities of potassium hydroxide solution. After 2 days the reaction mixture is heated for ½ hour at 50°C. After cooling the azo compound formed is precipitated by means of hydrochloric acid and filtered off.

References

Merck Index 8818
Kleeman & Engel p. 812
PDR pp. 830, 993, 1426, 1606
OCDS Vol. 2 p. 114 (1980)
I.N. p. 860
REM p. 1175
Askelof, E.E.A., Svartz, N. and Willstaedt, H.C.; U.S. Patent 2,396,145; March 5, 1946; assigned to A.B. Pharmacia (Sweden)

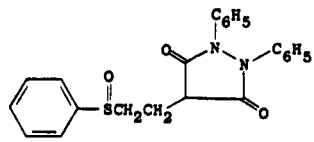
SULFINPYRAZONE

Therapeutic Function: Antiarthritic (uricosuric)

Chemical Name: 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57-96-5

Trade Name	Manufacturer	Country	Year Introduced
Anturane	Geigy	U.S.	1959
Anturan	Ciga Geigy	France	1960
Antazone	I.C.N.	Canada	–
Enturen	Geigy	Italy	–
Novopyrazone	Novopharm	Canada	–
Pyrocard	Trima	Israel	–
Zynol	Horner	Canada	–

Raw Materials

Hydrazobenzene
(β-Phenylmercaptoethyl)malonic acid diethyl ester
Sodium
Ethanol

Manufacturing Process

296 parts of (β-phenylmercapto-ethyl)-malonic acid diethyl ester and then 203 parts of hydrazobenzene are added while stirring to a warm sodium ethylate solution obtained from 23 parts of sodium and 400 parts by volume of absolute alcohol. About half the alcohol is then distilled off, after which 200 parts by volume of absolute xylene are gradually added without removing the inclined condenser. The temperature of the oil bath is kept at about 130°C for 12 hours while continuously stirring so that the alcohol still present and that which is liberated distills off but the xylene remains as solvent.

After cooling, 400 parts by volume of water are stirred in. The aqueous layer is separated from the xylene, shaken out twice with 40 parts by volume of chloroform and then made acid to Congo red paper with concentrated hydrochloric acid. The oil which separates is taken up in ethyl acetate and the solution obtained is washed with water. After drying over sodium sulfate the solvent is distilled off under reduced pressure and the residue is recrystallized from alcohol. 1,2-diphenyl-3,5-dioxo-4-(β-phenylmercapto-ethyl)-pyrazolidine melts at 106° to 108°C.

References

Merck Index 8828
Kleeman & Engel p. 845
PDR pp. 788, 830, 1606, 1999
OCDS Vol. 1 p. 238 (1977)
DOT 15 (2) 61 (1979)
I.N. p. 907
REM p. 1115
Häfliger, F.; U.S. Patent 2,700,671; January 25, 1955; assigned to J.R. Geigy AG, Switzerland

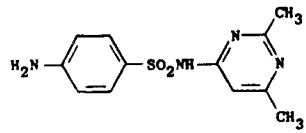
SULFISOMIDINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(2,6-dimethyl-4-pyrimidinyl)benzenesulfonamide

Common Name: Sulfadimetine, sulfaisodimidine, sulfasomidine

Structural Formula:



Chemical Abstracts Registry No.: 515-64-0

Trade Name	Manufacturer	Country	Year Introduced
Elkosin	Ciba	U.S.	1951
Elosine	Ciba Geigy	France	1953
Aristamid	Nordmark	W. Germany	–
Domion	Dainippon	Japan	–
Entamidine	Nippon Shoji	Japan	–
Isosulf	A.L.	Norway	–
Sulfamethin	Chemiek. Bitterfeld	E. Germany	–

Raw Materials

6-Amino-2,4-dimethylpyrimidine
p-Nitrobenzenesulfonyl chloride
Iron
Hydrogen chloride

Manufacturing Process

This starting material can be prepared as follows. 123 parts of finely powdered 6-amino-2,4-dimethylpyrimidine are suspended in 250 parts of dry pyridine and 222 parts of p-nitrobenzenesulfonyl chloride added at 50°C to 55°C. The whole is then warmed for 2 hours to 55°C. Water is added to the crystalline aggregate obtained, the precipitated bis-N-(p-nitrobenzenesulfonyl)-6-amino-2,4-dimethylpyrimidine filtered off by suction and washed with water. It is purified by recrystallizing from methyl ethyl ketone. On slowly heating it decomposes; on rapidly heating it melts at about 210°C to 215°C with decomposition.

49.3 parts of bis-N-(p-nitrobenzenesulfonyl)-6-amino-2,4-dimethylpyrimidine are heated to boiling for one hour with 12.3 parts of 6-amino-2,4-dimethylpyrimidine in 50 parts of dry pyridine. After cooling, the 6-(p-nitrobenzenesulfonamido)-2,4-dimethylpyrimidine formed is precipitated with water and filtered off by suction. It is purified by dissolving in dilute caustic soda and precipitating with acid. On recrystallization from dilute alcohol it melts (with decomposition) at 188°C to 189°C.

On reaction, for example, with iron and hydrochloric acid, 6-(p-aminobenzenesulfonamido)-2,4-dimethylpyrimidine, melting point 236°C is obtained.

References

Merck Index 8831
Kleeman & Engel p. 846
I.N. p. 907
Hartmann, M., von Meyenburg, H. and Druey, J.; U.S. Patent 2,429,184; October 14, 1947; assigned to Ciba Pharmaceutical Products, Inc.

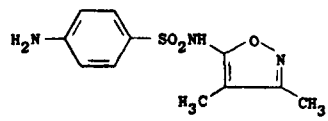
SULFISOXAZOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide

Common Name: Sulfafurazole

Structural Formula:



Chemical Abstracts Registry No.: 127-69-5

Trade Name	Manufacturer	Country	Year Introduced
Gantrisin	Roche	U.S.	1949
Unisulf	Lemmon	U.S.	1964
Entusul	U.S.V.	U.S.	1964
Sosol	Mc Kesson	U.S.	1970
SK-Soxazole	SKF	U.S.	1971
Soxomide	Upjohn	U.S.	1972
Sulfalar	Parke Davis	U.S.	1973
Soxo	Sutcliff/Case	U.S.	1974
Koro-Sulf	Holland Rantos	U.S.	1978
Amidoxal	Polfa	Poland	—
Azo-Gantrisin	Roche	U.S.	—
Dow-Sulfisoxazole	Dow	U.S.	—
Gansol	Abdi Ibrahim	Turkey	—
Isoxamin	Fuso	Japan	—
Novosoxazole	Novopharm	Canada	—
Pancid	Lister	Italy	—
Pediazole	Ross	U.S.	—
Sulfagan	Ohio Medical	U.S.	—
Sulfagen	Verdun	Canada	—
Sulfapolar	Farmos	Finland	—
Sulfazin	Shionogi	Japan	—
Sulfazole	Protea	Australia	—
Sulfizole	I.C.N.	Canada	—
Sulfoxol	Neopharma	Finland	—
Sulsoxin	Reid-Provident	U.S.	—
Thiasin	Yamanouchi	Japan	—
TL-Azole	Zenith	U.S.	—
Urazole	Propan-Lipworth	S. Africa	—
Urogan	Adams	Australia	—
U.S.-67	Saunders	Canada	—
V-Sul	Vangard	U.S.	—

Raw Materials

3,4-Dimethyl-5-aminoisoxazole
p-Acetaminobenzene sulfonic acid chloride
Hydrogen chloride

Manufacturing Process

112 parts of 3,4-dimethyl-5-amino-isoxazole were dissolved in a mixture of 100 volume parts of pyridine and 200 volume parts of acetone. The mixture is cooled with cold water and 240 parts p-acetamino-benzene sulfonic acid chloride are added in small portions under stirring at temperatures of below 30°C. The mixture is left standing overnight at 20° to 30°C and then the 5-acetamino-benzene-sulfonylamino-3,4-dimethyl-isoxazole is precipitated by the addition of water. Recrystallized from acetic acid or alcohol it forms small prisms of the melting point 210°C.

100 parts of the 5-acetamino-benzene-sulfonyl-amino-3,4-dimethyl-isoxazole are boiled under reflux with 500 volume parts 15 to 20% aqueous hydrochloric acid for 30 to 45 minutes until all is dissolved. 500 parts crystallized sodium acetate are added and the liquid left cooling for crystallization. The sulfanilamido-3,4-dimethyl-isoxazole is sucked off, washed with water and dried. In the pure state it forms white prisms with the melting point of 193°C.

References

Merck Index 8832
Kleeman & Engel p. 837
PDR pp. 1473, 1487, 1558, 1606, 1999
OCDS Vol. 1 p. 124 (1977)
I.N. p. 900
REM p. 1175
Wuest, H.M. and Hoffer, M.; U.S. Patent 2,430,094; November 4, 1947; assigned to Hoffmann-La Roche, Inc.

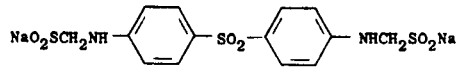
SULFOXONE SODIUM

Therapeutic Function: Antibacterial (leprostatic)

Chemical Name: Disodium[sulfonylbis(p-phenylenimino)] dimethanesulfinate

Common Name: Aldesulfone sodium

Structural Formula:



Chemical Abstracts Registry No.: 144-75-2

Trade Name	Manufacturer	Country	Year Introduced
Diasone Sodium	Abbott	U.S.	1947

Raw Materials

Diaminodiphenyl sulfone
Sodium formaldehyde sulfoxylate

Manufacturing Process

About 20 grams of diamino diphenyl sulfone is dissolved in about 500 cc of ethyl alcohol (3A made up of 5 parts methyl alcohol and 100 parts of ethyl alcohol) by placing the ingredients in a flask provided with a reflux condenser and warming over a water bath. About 24 grams of pure grade, very finely powdered (40 to 60 mesh) sodium formaldehyde sulfoxylate is then rapidly added to the alcohol solution of diamino diphenyl sulfone and the mixture refluxed in the usual manner. It was found that the mixture should be refluxed for a total of 5 hours and that a precipitate starts to form near the 3 hour period. The reaction mixture is then cooled to 15°C and kept at this temperature for about 1 hour. The precipitate formed in the filtrate is filtered off rapidly and drained as much as possible to remove mother liquor and then washed with small amounts of cold alcohol. The solid product is immediately placed in a desiccator and dried over sulfuric acid for about 20 hours.

References

Merck Index 8848
Kleeman & Engel p. 847
OCDS Vol. 1 p. 140 (1977)
I.N. p. 51
REM p. 1217
Rosenthal, S.M. and Bauer, H.; U.S. Patent 2,234,981; March 18, 1941; assigned to the U.S. Secretary of the Treasury
Raiziss, G.W., Clemence, L.R.W. and Freifelder, M.; U.S. Patent 2,256,575; September 23, 1941; assigned to Abbott Laboratories

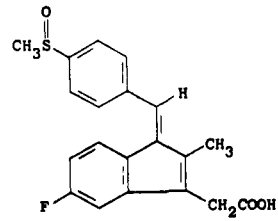
SULINDAC

Therapeutic Function: Antiinflammatory

Chemical Name: (Z)-5-fluoro-2-methyl-1[[4-(methylsulfinyl)phenyl] methylene]-1H-indene-3-acetic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 38194-50-2

Trade Name	Manufacturer	Country	Year Introduced
Imbaral	Sharp & Dohme	W. Germany	1976
Clinoril	MSD	Italy	1976
Arthrocine	Chibret	France	1977
Clinoril	MSD	U.K.	1977
Clinoril	MSD	U.S.	1978
Clinoril	Banyu	Japan	1982
Clinoril	Kyorin	Japan	1982
Aflodac	Benvegna	Italy	1982
Algocetil	Francia	Italy	—
Citireuma	C.T.	Italy	—
Lyndak	Tiber	Italy	—
Mobilin	Teva	Israel	—
Reumofil	Ausonia	Italy	—
Sudac	Errekappa	Italy	—
Sulene	Scalari	Italy	—
Sulic	Crosara	Italy	—
Sulinol	Farnex	Italy	—

Raw Materials

p-Fluorobenzaldehyde

Propionic anhydride

Hydrogen
p-Methylthiobenzaldehyde
Sodium periodate
Polyphosphoric acid
Cyanacetic acid

Manufacturing Process

The following process sequence is described in U.S. Patent 3,654,349:

p-Fluoro-α-Methylcinnamic Acid: 200 grams (1.61 mols) p-fluorobenzaldehyde, 3.5 grams (2.42 mols) propionic anhydride and 155 grams (1.61 mols) sodium propionate are mixed in a 1 liter three-necked flask which had been flushed with nitrogen. The flask is heated gradually in an oil-bath to 140°C. After 20 hours the flask is cooled to 100°C and the contents are poured into 8 liters of water. The precipitate is dissolved by adding 302 grams potassium hydroxide in 2 liters of water. The aqueous solution is extracted with ether, and the ether extracts washed with potassium hydroxide solution. The combined aqueous layers are filtered, acidified with concentrated HCl, filtered and the collected solid washed with water, thereby producing p-fluoro-α-methylcinnamic acid which is used as obtained.

p-Fluoro-α-Methylhydrocinnamic Acid: To 177.9 grams (0.987 mol) p-fluoro-α-methylcinnamic acid in 3.6 liters ethanol is added 11.0 grams of 5% Pd/C and the mixture reduced at room temperature under a hydrogen pressure of 40 psi. Uptake is $^{31}/_{32}$ pounds (97% of theoretical). After filtering the catalyst, the filtrate is concentrated in vacuo to give the product p-fluoro-α-methylhydrocinnamic acid used without weighing in next step.

6-Fluoro-2-Methylindanone: To 932 grams polyphosphoric acid at 70°C on the steam bath is added 93.2 grams (0.5 mol) p-fluoro-α-methylhydrocinnamic acid slowly with stirring. This temperature is gradually raised to 95°C and the mixture kept at this temperature for 1 hour. The mixture is allowed to cool and added to 2 liters of water. The aqueous layer is extracted with ether, the ether solution washed twice with saturated sodium chloride solution, 5% Na_2CO_3 solution, water, and then dried. The ether filtrate is concentrated with 200 grams silica-gel, and added to a five pound silica-gel column packed with 5% ether-petroleum ether. The column is eluted with 5 to 10% ether-petroleum ether and followed by TLC to give 6-fluoro-2-methylindanone.

5-Fluoro-2-Methylindene-3-Acetic Acid: A mixture of 18.4 grams (0.112 mol) of 6-fluoro-2-methylindanone, 10.5 grams (0.123 mol) cyanacetic acid, 6.6 grams acetic acid and 1.7 grams ammonium acetate in 15.5 ml dry toluene is refluxed with stirring for 21 hours, as the liberated water is collected in a Dean Stark trap. The toluene is concentrated and the residue dissolved in 60 ml of hot ethanol and 14 ml of 2.2 N aqueous potassium hydroxide solution. 22 grams of 85% KOH in 150 ml of water is added and the mixture refluxed for 13 hours under N_2. The ethanol is removed under vacuum, 500 ml water added, the aqueous solution washed well with ether and then boiled with charcoal. The aqueous filtrate is acidified to pH 2 with 50% hydrochloric acid, cooled and the precipitate collected In this way dried 5-fluoro-2-methyl-indenyl-3-acetic acid (MP 164° to 166°C) is obtained.

5-Fluoro-2-Methyl-1-(p-Methylthiobenzylidene)-3-Indenylacetic Acid: 15 grams (0.072 mol) 5-fluoro-2-methyl-3-indenylacetic acid, 14.0 grams (0.091 mol) p-methylthiobenzaldehyde and 13.0 grams (0.24 mol) sodium methoxide are heated in 200 ml methanol at 60°C under nitrogen with stirring for 6 hours. After cooling the reaction mixture is poured into 750 milliliters of ice-water, acidified with 2.5 N hydrochloric acid and the collected solid triturated with a little ether to produce 5-fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic acid (MP 187° to 188.2°C).

5-Fluoro-2-Methyl-1-(p-Methylsulfinylbenzylidene)-3-Indenylacetic Acid: To a solution of 3.4 grams (0.01 mol) 5-fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic acid in a 250 ml mixture of methanol and 100 ml acetone is added a solution of 3.8 grams (0.018 mol) of sodium periodate in 50 ml water with stirring.

450 ml water is added after 18 hours and the organic solvents removed under vacuum below

30°C. The precipitated product is filtered, dried and recrystallized from ethyl acetate to give 5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-3-indenylacetic acid. Upon repeated recrystallization from ethylacetate there is obtained cis-5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-3-indenylacetic acid (MP 184° to 186°C).

References

Merck Index 8863
Kleeman & Engel p. 847
PDR p. 1147
OCDS Vol. 2 p. 210 (1980)
DOT 12 (2) 496 (1976)
I.N. p. 909
REM p. 1120
Hinkley, D.F. and Conn, J.B.; U.S. Patent 3,647,858; March 7, 1972; assigned to Merck & Co., Inc.
Shen, T.-Y., Greenwald, R.B., Jones, H., Linn, B.O. and Witzel, B.E.; U.S. Patent 3,654,349; April 4, 1972; assigned to Merck & Co., Inc.

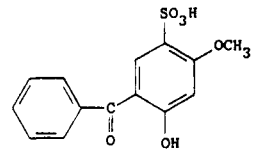
SULISOBENZONE

Therapeutic Function: Ultraviolet screen

Chemical Name: 5-Benzoyl-4-hydroxy-2-methoxybenzenesulfonic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 4065-45-6

Trade Name	Manufacturer	Country	Year Introduced
Uval	Dome	U.S.	1965
Cyasorb	Cyanamid	U.S.	—
Spectra-Sorb	Cyanamid	U.S.	—
Sungard	Miles	U.S.	—
Uvinul	G.A.F.	U.S.	—

Raw Materials

2-Hydroxy-4-methoxybenzophenone
Chlorosulfonic acid

Manufacturing Process

663 g of dichloroethane and 74.6 g 2-hydroxy-4-methoxybenzophenone were charged into a 3-neck flask equipped with stirrer, thermometer, reflux condenser and dropping funnel and a heating mantle. The solution was heated to the reflux temperature (85°C to 86°C) and was dehydrated by distilling off 66.5 g 1,2-dichloroethane. While maintaining at reflux, 30 g chlorosulfonic acid was added slowly over a period of about two hours. The rate of addition was

regulated by the speed of evolution of the HCl. After all the chlorosulfonic acid was added, the charge was still maintained at reflux for an additional 15 minutes to remove traces of HCl. It was then cooled to 5°C and filtered. The filter cake was washed with 500 g cold 1,2-dichloroethane and dried. 98 g of product were obtained.

References

Merck Index 8865
I.N. p. 909
Cofrancesco, A.J.; British Patent 1,136,525; December 11, 1968; assigned to General Aniline & Film Corp.

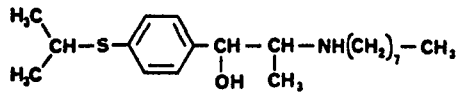
SULOCTIDIL

Therapeutic Function: Spasmolytic, vasodilator

Chemical Name: 1-(4-Isopropylthiophenyl)-2-n-octylaminopropanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 54063-56-8

Trade Name	Manufacturer	Country	Year Introduced
Sulocton	Cooper	Switz.	1978
Flavisco	Searle	France	1980
Locton	Lepetit	Italy	1980
Fluversin	Searle	W. Germany	1980
Bemperil	Sidus	Argentina	–
Cerebro	Sidus	Italy	–
Circleton	I.B.I.	Italy	–
Dulasi	Durron	Italy	–
Duloctil	Searle	U.K.	–
Euvasal	Selvi	Italy	–
Ibisul	I.B.I.	Italy	–
Locton	Lepetit	Italy	–
Polivasal	Coli	Italy	–
Sudil	Errekappa	Italy	–
Sulc	Tosi	Italy	–
Sulodene	Alfa Farm.	Italy	–
Suloktil	Yurtoglu	Turkey	–
Sutidil	Krka	Yugoslavia	–
Tamid	Serpero	Italy	–

Raw Materials

α-Bromo-4-isopropylthiopropiophenone
n-Octylamine
Sodium borohydride

Manufacturing Process

(a) To 28.7 g of α-bromo-4-isopropylthiopropiophenone (0.1 mol) in 100 ml of isopropanol there are rapidly added 14.2 g of n-octylamine while stirring, and then the mixture is brought to 80°C for 1 hour. The solvent is evaporated under vacuum, the residue is diluted with 1 liter of ether and is left to stand overnight in the refrigerator. The precipitate obtained is filtered and dried. There are thus obtained 25 g of α-n-octylamino-4-isopropylthiopropiophenone hydrobromide. Yield: 60%; melting point: 162°C to 164°C.

(b) 41.6 g of the preceding product (0.1 mol) in 200 ml of methanol are cooled in an ice bath to 0°C. There is added drop by drop while stirring a solution of 4.1 g of $NaBH_4$ in 50 ml of water and 2 ml of 5% NaOH. Next, the mixture is stirred for 2 hours at room temperature. The methanol is evaporated under vacuum, diluted with 200 ml of water and extracted with methylene chloride or ether. The organic phase is dried on $MgSO_4$ and the solvent is evaporated under vacuum. The oily residue obtained solidifies rapidly and is recrystallized in pentane. 33.2 g are thus obtained. Yield: 90%; melting point: 62°C to 63°C.

References

Merck Index 8870
Kleeman & Engel p. 849
OCDS Vol. 3 p. 26 (1984)
DOT 13 (3) 107 (1977)
I.N. p. 910
Lambelin, G.E., Gillet, C.L. and Roba, J.L.; U.S. Patent 4,228,187; October 14, 1980; assigned to Continental Pharma

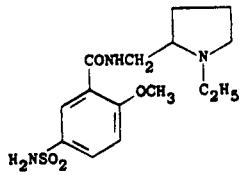
SULPIRIDE

Therapeutic Function: Tranquilizer; digestive aid

Chemical Name: 5-(aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl] -2-methoxybenzamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 15676-16-1

Trade Name	Manufacturer	Country	Year Introduced
Dogmatil	Delagrange	France	1969
Dogmatil	Schurholz	W. Germany	1972
Dogmatil	Delagrange	Italy	1972
Dogmatil	Delagrange	Switz.	1972
Dogmatil	Fujisawa	Japan	1973
Dogmatil	Squibb	U.K.	1983
Abilit	Sumitomo	Japan	–
Betamac	Sawai	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Chamionil	Vita	Italy	—
Coolspan	Hishiyama	Japan	—
Digton	Areu	Spain	—
Dobren	Ravizza	Italy	—
Eglonyl	Alkaloid	Yugoslavia	—
Equilid	Lepetit	Italy	—
Eusulpid	C.T.	Italy	—
Guastil	Uriach	Spain	—
Isnamide	Isardi	Italy	—
Kapiride	Kappa	Spain	—
Lavodina	Turro	Spain	—
Lusedan	Bryan	Spain	—
Meresa	Dolorgiet	W. Germany	—
Miradol	Mitsui	Japan	—
Misulvan	Bernabo	Argentina	—
Modal	Rafa	Israel	—
Neogama	Hormosan	W. Germany	—
Neuromyfar	Emyfar	Spain	—
Normum	Serpero	Italy	—
Omperan	Taiho	Japan	—
Paratil	Medica	Finland	—
Psicosen	Centrum	Spain	—
Pyrikappl	Isei	Japan	—
Quiridil	Zoja	Italy	—
Sato	Scharper	Italy	—
Seeglu	Teikoku	Japan	—
Sicofrenol	Basileos	Spain	—
Sulpiril	Leiras	Finland	—
Sulpisidan	Llano	Spain	—
Suprium	Orion	Finland	—
Sursumid	Sarm	Italy	—
Tepavil	Prodes	Spain	—
Tonofit	Europa	Spain	—
Trilan	Esseti	Italy	—
Ulpir	Lesvi	Spain	—
Vipral	Roemmers	Argentina	—

Raw Materials

1-Ethyl-2-aminomethylpyrrolidine
2-Methoxy-5-sulfamylbenzoic acid

Manufacturing Process

1-Ethyl-2-aminomethylpyrrolidine is reacted with 2-methoxy-5-sulfamoylbenzoic acid to give sulpiride.

References

Merck Index 8875
Kleeman & Engel p. 849
OCDS Vol. 2 p. 94 (1980)
DOT 9 (6) 244 (1973)
I.N. p. 911
Miller, C.S., Engelhardt, E.L. and Thominet, M.L.; U.S. Patent 3,342,826; Sept. 19, 1967; assigned to Societe d'Etudes Scientifiques et Industrielles de l'Ile-de-France, France

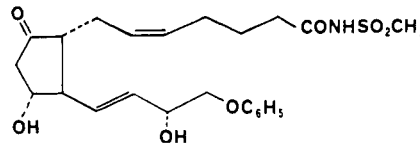
SULPROSTONE

Therapeutic Function: Fertility control

Chemical Name: N-Methanesulfonyl-9-oxo-11α,15α-dihydroxy-5-cis-13-trans-16-phenoxy-ω-tetranorprostadienamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 60325-46-4

Trade Name	Manufacturer	Country	Year Introduced
Nalador	Schering	W. Germany	1981
Nalador	Schering	Switz.	1983

Raw Materials

(4-Carbohydroxy-n-butyl)triphenylphosphonium bromide
Sodium methylsulfinylmethide
2-[5α-Hydroxy-3α(tetrahydropyran-2-yloxy)-2β-(3α-tetrahydropyran-2-yloxy-4-phenoxy-trans-1-buten-1-yl)cyclopent-1α-yl] -acetaldehyde α-hemiacetal
Chromic anhydride
Methanesulfonyl isocyanate
Acetic acid

Manufacturing Process

9α-Hydroxy-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid: To a solution of 1.6 g (3.6 mmols) (4-carbohydroxy-n-butyl)triphenylphosphonium bromide in a dry nitrogen atmosphere in 6.0 ml dry dimethyl sulfoxide was added 3.24 ml (6.5 mmols) of a 2.0 M solution of sodium methylsulfinylmethide in dimethyl sulfoxide. To this red ylide solution was added dropwise a solution of 613 mg (1.29 mmols) 2-[5α-hydroxy-3α-(tetrahydropyran-2-yloxy)-2β-(3α-tetrahydropyran-2-yloxy-4-phenoxy-trans-1-buten-1-yl)cyclopent-1α-yl] acetaldehyde, γ-hemiacetal in 5.0 ml dry dimethyl sulfoxide over a period of 20 minutes.

After an additional 2 hours stirring at room temperature, the reaction mixture was poured onto ice water. The basic aqueous solution was washed twice with ethyl acetate (20 ml) and acidified to pH 3 with 10% aqueous hydrochloric acid.

The acidic solution was extracted with ethyl acetate (3 x 20 ml) and the combined organic extracts washed once with water (10 ml), dried ($MgSO_4$) and evaporated to a solid residue. This solid residue was triturated with ethyl acetate and the filtrate concentrated. Yield: 754 mg of 9α-hydroxy-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid was collected.

9-Oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid: To a solution cooled to -10°C under nitrogen of 754 mg (1.3 mmols) 9α-hydroxy-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid in 13 ml reagent grade acetone was added dropwise to 0.56 ml (1.41 mmols) of Jones' reagent (chromic anhydride). After 20 minutes at -10°C, 0.260 ml 2-propanol was

added and the reaction mixture was allowed to stir an additional 5 minutes at which time it was combined with 75 ml ethyl acetate, washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to give 752 mg of 9-oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid, which was chromatographed on silica gel using ethyl acetate as eluent to afford 505 mg of pure intermediate.

N-Methanesulfonyl-9-oxo-11α,15α-dihydroxy-5-cis-13-trans-16-phenoxy-ω-tetranorprostadienamide: To 1.0 mmols of 9-oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid in 40 ml THF is added 2 ml triethylamine. After 15 minutes of stirring at room temperature 10.0 ml of 0.1 M methanesulfonylisocyanate in THF is added. After a further 1 hour of stirring, the reaction mixture is neutralized with acetic acid and the solvent removed by evaporation (in vacuo). The resultant residue is taken up in methylene chlorine and washed successively with water and sodium bicarbonate to yield, after drying and solvent evaporation, N-methanesulfonyl-9-oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienamide. This intermediate is then hydrolyzed overnight with acetic acid/water and purified by column chromatography to give the desired N-methanesulfonyl-9-oxo-11α,15α-dihydroxy-5-cis-13-trans-16-phenoxy-ω-tetranorprostadienamide.

References

Merck Index 8877
DFU 3 (1) 59 (1978)
OCDS Vol. 3 p. 9 (1984)
DOT 18 (7) 331 (1982)
I.N. p. 911
Bindra, J.S. and Johnson, M.R.; U.S. Patents 4,024,179; May 17, 1977; and 4,244,887; January 13, 1981; both assigned to Pfizer, Inc.

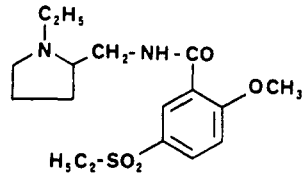
SULTOPRIDE HYDROCHLORIDE

Therapeutic Function: Neuroleptic

Chemical Name: N-(1-Ethyl-2-pyrrolidylmethyl)-2-methoxy-5-ethylsulfonylbenzamide hydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 53583-79-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Barnetil	Delagrange	France	1976
Barnotil	Vita	Italy	1983
Topral	Alkaloid	Yugoslavia	—

Raw Materials

N-Ethyl-α-aminomethylpyrrolidine
Phosphorus trichloride
2-Methoxy-5-ethylsulfonylbenzoic acid

Manufacturing Process

A solution of 17.22 g of N-ethyl-α-aminomethylpyrrolidine in 360 ml of pyridine is placed in a 1 ℓ balloon flask. A solution of 3.51 g of phosphorus trichloride in 40 ml of pyridine is added at ambient temperature. After the mixture has been stirred for 1 hour, 10 g of 2-methoxy-5-ethylsulfonylbenzoic acid is introduced. The mixture is heated under reflux for 4½ hours. After cooling, the solvent is evaporated under vacuum and the residue is dissolved in 200 ml of 20% sodium hydroxide. The solution is extracted with 200 ml of chloroform.

The organic solution is dried and filtered and the solvent is evaporated under vacuum; the residue is dissolved in 150 ml of ethanol and the solution is acidified with hydrochloric acid. The hydrochloride is dried without heating and recrystallized from 100 ml of absolute ethanol. 7.2 g of N-(1-ethyl-2-pyrrolidyl-methyl-2-methoxy-5-ethylsulfonylbenzamide hydrochloride is produced. Melting point: 190°C to 193°C.

References

Merck Index 8879
DFU 1 (2) 83 (1976)
Kleeman & Engel p. 851
DOT 13 (4) 154 (1977)
I.N. p. 911
Societe D'Etudes Scientifiques et Industrielles de L'Ile-de-France; British Patent 1,394,559; May 21, 1975

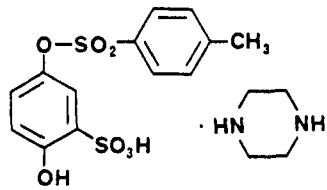
SULTOSILIC ACID PIPERAZINE SALT

Therapeutic Function: Hypolipemic

Chemical Name: 2-Hydroxy-5-[[(4-methylphenyl)sulfonyl] oxy] benzenesulfonic acid, piperazine salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57775-27-6; 57775-26-5 (Free acid)

Trade Name	Manufacturer	Country	Year Introduced
Mimedran	Esteve	Spain	1982

Raw Materials

2,5-Dihydroxybenzenesulfonic acid
Pyridine
Tosyl chloride
Piperazine

Manufacturing Process

The monotosylation of 2,5-dihydroxybenzenesulfonic acid is carried out in a pyridine medium by treating it with tosyl chloride, thus preferably isolating the 2-hydroxy-5-tosyloxybenzenesulfonic acid, pyridine salt. This product subjected to reflux with an alcoholic solution of piperazine yields 2-hydroxy-5-tosyloxybenzenesulfonic acid, piperazine salt.

References

DFU 6 (11) 688 (1981)
Esteve-Subirana, A.; U.S. Patent 3,954,767; May 4, 1976

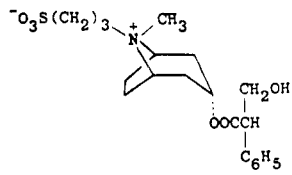
SULTROPONIUM

Therapeutic Function: Antispasmodic

Chemical Name: Endo(±)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(3-sulfopropyl)-8-azoniabicyclo[3.2.1]octane hydroxide, inner salt

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 15130-91-3

Trade Name	Manufacturer	Country	Year Introduced
Sultroponium-B	Biotherax	France	1970

Raw Materials

Atropine
Propane-1,3-sultone

Manufacturing Process

To a cold solution of 29 g of atropine in 250 ml of acetone a solution of 13 g of propane-1,3-sultone in 100 ml of acetone is generally added. The combined solution is left for 48 hours. The white precipitate of fine crystalline needles is separated, washed several times with acetone, and then recrystallized from ethanol. It melts at 220°C.

References

Merck Index 8880
Kleeman & Engel p. 851
DOT 6 (3) 97 (1970)
I.N. p. 912
Raudnitz, J.P.M. and Wahl, H.; British Patent 1,082,445; September 6, 1967

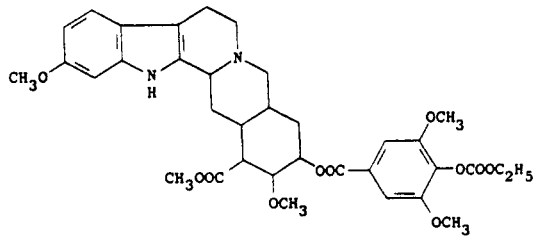
SYROSINGOPINE

Therapeutic Function: Antihypertensive

Chemical Name: 18-[[4-[(Ethoxycarbonyl)oxy]-3,5-dimethoxybenzoyl] oxy]-11,17-dimethoxyyohimban-16-carboxylic acid methyl ester

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 84-36-6

Trade Name	Manufacturer	Country	Year Introduced
Singoserp	Ciba	U.S.	1958
Syringia	Toyo Jozo	Japan	1975
Aurugopin	Nisshin	Japan	—
Elumonon	Tatsumi	Japan	—
Hipotensor Zambe	Zambeletti	Italy	—
Neoreserpan	Panthox & Burck	Italy	—
Nichiserpine-S	Nichiiko	Japan	—
Novoserpina	Ghimas	Italy	—
Raunova	Zambeletti	Italy	—
Rosidil	Nippon Chemiphar	Japan	—
Siroshuten	Isei	Japan	—
Tesamurin	Zensei	Japan	—

Raw Materials

Methyl reserpate
O-Carbethoxysyringoyl chloride

Manufacturing Process

1 part by weight of methyl reserpate and 1.9 parts by weight of O-carbethoxysyringoyl chloride were dissolved in 20 parts by volume of anhydrous pyridine and allowed to stand at 5°C for 3 days. An equal volume of ice was then added, and the mixture evaporated to dryness in vacuo. The residue was dissolved in 50 parts by volume of chloroform and washed in succession with three 50 parts by volume portions of 2% sodium hydroxide solution and two 50 parts by volume portions of water. The chloroform solution was dried over sodium sulfate and evaporated to dryness. The residue was dissolved in 15 parts by volume of benzene and chromatographed on a 10 part by weight column of II-III grade alumina. Eluates of benzene, 90 benzene: 10 acetone, 80 benzene: 20 acetone, 60 benzene: 40 acetone; and acetone were removed. From the 90 benzene: 10 acetone eluate there was recovered crystalline methyl O-(O'-carbethoxysyringoyl)-reserpate, melting point 175°C to 178°C, on crystallization from acetone.

References

Merck Index 8901

Kleeman & Engel p. 853
OCDS Vol. 1 p. 319 (1977)
I.N. p. 917
Lucas, R.A.; U.S. Patent 2,813,871; November 19, 1957; assigned to Ciba Pharmaceutical Products, Inc.