product occurred in the form of colorless crystals soluble in dilute alkaline solutions, alcohol and ether and insoluble in water.

References

Merck Index 9266
Kleeman & Engel p. 882
DOT 12 (6) 238 (1976)
I.N. p. 38
Clemence, F. and Le Martret, O.; U.S. Patent 4,159,986; July 3, 1979; assigned to Roussel Uclaf (France)

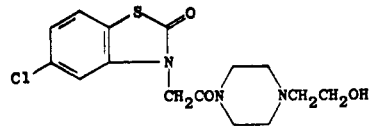
TIARAMIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 4-[(5-chloro-2-oxo-3(2H)-benzothiazolyl)acetyl]-1-piperazineethanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 32527-55-2; 35941-71-0 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Solantal	Fujisawa	Japan	1975
Ventaval	Crinos	Italy	1981
Royzolon	Sawai	Japan	–

Raw Materials

Ethyl 5-chloro-2-oxobenzothiazoline acetate
1-(2-Hydroxyethyl)piperazine

Manufacturing Process

A solution of ethyl 5-chloro-2-oxo-3-benzo-thiazolineacetate (4.0 grams) in 1-(2-hydroxyethyl)piperazine is heated at 100°C for 24 hours. After cooling, the resulting mixture is extracted with chloroform. The chloroform extract is washed with water and shaken with 10% hydrochloric acid. The hydrochloric acid layer is washed with chloroform, made alkaline with 10% sodium hydroxide solution and extracted with chloroform. The chloroform extract is washed with water, dried over magnesium sulfate and concentrated. The residual oil (5.5 grams) is allowed to stand to form crystals, which are recrystallized from a mixture of ethyl acetate (40 ml) and ethanol (15 ml) to give 3-[4-(2-hydroxyethyl)-1-piperazinylcarbonylmethyl]-5-chloro-2(3H)-benzothiazolinone (3.2 grams) as colorless crystals, MP 159° to 161°C.

The following is an alternate method of preparation: A mixture of 3-(1-piperazinyl)carbonylmethyl-5-chloro-2(3H)-benzothiazolinone (500 mg), anhydrous potassium carbonate (400 mg), 2-hydroxyethyl bromide (300 mg) and anhydrous ethanol (20 ml) is heated while refluxing for 5 hours. The reaction mixture is concentrated under reduced pressure. The residue is extracted with chloroform. The chloroform layer is dried over magnesium

sulfate and concentrated. The residue is crystallized from a mixture of ethyl acetate and ethanol to give 3-[4-(2-hydroxyethyl]-1-piperazinylcarbonylmethyl]-5-chloro-2(3H)-benzothiazolinone (370 mg) as crystals, MP 159° to 160°C.

References

Merck Index 9268
Kleeman & Engel p. 882
DOT 9 (9) 390 (1973)
I.N. p. 949
Umio, S.; U.S. Patent 3,661,921; May 9, 1972; assigned to Fujisawa Pharmaceutical Co., Ltd., Japan

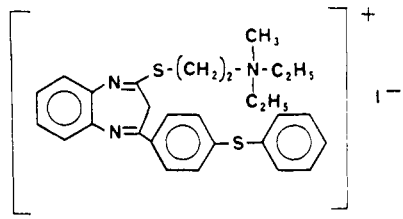
TIBEZONIUM IODIDE

Therapeutic Function: Antimicrobial

Chemical Name: 2β-N-Diethylaminoethylthio-4-p-phenylthiophenyl-3H-1,5-benzodiazepine iodomethylate

Common Name: Thiabenzazonium iodide

Structural Formula:



Chemical Abstracts Registry No.: 54663-47-7

Trade Name	Manufacturer	Country	Year Introduced
Antoral	Recordati	Italy	1977

Raw Materials

4-Acetyldiphenylsulfide
o-Phenylenediamine
Methyl iodide
Carbon disulfide
β-Dimethylaminoethyl chloride

Manufacturing Process

4-Acetyldiphenylsulfide is reacted with carbon disulfide in an initial step to give 4-phenylthiobenzoyl dithioacetic acid. That, in turn, is reacted with o-phenylenediamine.

A mixture of 3.6 g of the thus obtained 4-p-phenylthiophenyl-1,3-dihydro-2H-1,5-benzodiazepine-2-thione, 0.50 g of 50% sodium hydride in oil and 200 ml of benzene is refluxed for 30 minutes, then a solution of 2.02 g of β-diethylaminoethyl chloride in 5 ml of benzene are added dropwise over 5 minutes.

The mixture is refluxed for 10 hours. The mixture is then cooled and filtered to separate the sodium chloride. The filtrate is evaporated to dryness in vacuo. The oily residue is dissolved

in petroleum ether and the solution is filtered with charcoal. The solvent is evaporated in vacuo. The oily residue is heated to 50°C in vacuo (0.01 mm Hg) to remove the excess of β-diethylaminoethyl chloride.

This treatment is continued until the β-diethylaminoethyl chloride disappears (TLC). The oil is then dissolved in isopropanol and weakly acidified with HCl in propanol. The 2β-N-diethylaminoethylthio-4-p-phenylthiophenyl-3H-1,5-benzodiazepine·HCl product crystallizes by addition of anhydrous ethyl ether to the solution. The crystals are filtered and recrystallized from ethyl acetate. Yield 3.65 g, melting point 150°C.

2.55 g of methyl iodide are added to a solution of 5.93 g of 2-β-N-diethylaminoethylthio-4-p-phenylthiophenyl-3H-1,5-benzodiazepine in 100 ml of isopropanol. The mixture is kept at 20°C to 30°C for 60 hours. The crystals are then filtered. Yield 6.2 g, melting point 161°C.

References

Merck Index 9269
DFU 3 (2) 152 (1978)
Kleeman & Engel p. 883
DOT 14 (6) 252 (1978)
I.N. p. 950
Nardi, D., Massarani, E. and Degen, L.; U.S. Patent 3,933,793; January 20, 1976; assigned to Recordati S.A. Chemical & Pharmaceutical Co.

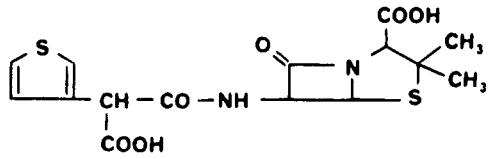
TICARCILLIN DISODIUM

Therapeutic Function: Antibiotic

Chemical Name: α-Carboxy-α-(3-thienyl)methyl penicillin disodium salt

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 4697-14-7; 3973-04-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ticar	Beecham	U.S.	1976
Aerugipen	Beecham-Woelfing	W. Germany	1977
Ticar	Beecham	U.K.	1979
Monapen	Fujisawa	Japan	1979
Ticarpenin	Beecham	Japan	1980
Ticalpenin	Beecham	Italy	1980
Ticar	Beecham	France	1981
Neoanabactyl	Beecham	–	–
Ticillin	C.S.L.	Australia	–
Timentin	Beecham	U.S.	–

Raw Materials

Monobenzyl-3-thienylmalonate

Thionyl chloride

6-Aminopenicillanic acid
Hydrogen
Sodium bicarbonate

Manufacturing Process

A mixture of monobenzyl-3-thienylmalonate (1.38 g, 5 mmol) and thionyl chloride (2.5 ml) was warmed at 50°C to 55°C for 1 hour, then at 60°C to 65°C for 10 minutes. The excess of thionyl chloride was removed in vacuo at not more than 30°C, the last traces being removed by codistillation with dry benzene (1 ml) under high vacuum, leaving monobenzyl-3-thienylmalonyl chloride as a yellow oil.

The acid chloride obtained as described above was dissolved in dry acetone (10 ml) and added in a steady stream to a stirred solution of 6-aminopenicillanic acid (1.08 g, 5 mmol) in a mixture of N sodium bicarbonate (15 ml) and acetone (5 ml). After the initial reaction the reaction mixture was stirred at room temperature for 45 minutes, then washed with ether (3 x 25 ml). Acidification of the aqueous solution with N hydrochloric acid (11 ml) to pH 2 and extraction with ether (3 x 15 ml) gave an ethereal extract which was decolorized with a mixture of activated charcoal and magnesium sulfate for 5 minutes.

The resulting pale yellow ethereal solution was shaken with sufficient N sodium bicarbonate (4 ml) to give an aqueous extract of pH 7 to 7.5. This extract was concentrated to syrup at low temperature and pressure, then isopropanol was added with stirring until the mixture contained about 10% water.

Crystallization was initiated, and completed at about 0°C overnight, to give the sodium salt of α-(benzyloxycarbonyl)-3-thienylmethylpenicillin as white crystals in 50% weight yield. This product was estimated by colorimetric assay with hydroxylamine to contain 91% of the anhydrous sodium salt.

A solution of the sodium salt of α-(benzyloxycarbonyl)-3-thienylmethylpenicillin (2.13 g, 4.3 mmol) in water (30 ml) was added to a suspension of 5% palladium on calcium carbonate (10.65 g) in water (32 ml) which had been prehydrogenated for 1 hour.

The mixture was then hydrogenated at just above atmospheric pressure for 1½ hours and filtered through a Dicalite bed. The clear filtrate was evaporated at low temperature and pressure, and the residue dried in vacuo over phosphorus pentoxide, to give 1.64 g of the salt of α-(3-thienyl)methylpenicillin as a white solid.

Colorimetric assay with hydroxylamine showed this salt to contain 94% of the anhydrous penicillin. Paper chromatography showed complete reduction of the benzyl group.

References

Merck Index 9271
Kleeman & Engel p. 883
PDR pp. 663, 666
OCDS Vol. 2 p. 437 (1980)
DOT 10 (2) 55 (1974); 11 (11) 446 (1975) & 13 (9) 374 (1977)
I.N. p. 950
REM p. 1199
Beecham Group, Ltd.; British Patent 1,125,557; August 28, 1968
Brain, E.G. and Nayler, J.H.C.; U.S. Patent 3,282,926; November 1, 1966; and U.S. Patent 3,492,291; January 27, 1970; both assigned to Beecham Group, Ltd.

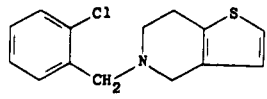
TICLOPIDINE HYDROCHLORIDE

Therapeutic Function: Platelet inhibitor

Chemical Name: 5-[(2-Chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 53885-35-1; 55142-85-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ticlid	Millot	France	1978
Tiklidan	Labaz	W. Germany	1980
Panaldin	Daiichi Seiyaku	Japan	1981
Tiklid	Midy	Italy	1981
Ticlodone	Crinos	Italy	1982
Caudaline	Exa	Argentina	–

Raw Materials

Thieno[3,2-c]pyridine
Sodium borohydride
2-Chlorobenzyl chloride
Hydrogen chloride

Manufacturing Process

A solution of thieno[3,2-c]pyridine (13.5 g; 0.1 mol) and 2-chlorobenzyl chloride (17.7 g) in acetonitrile (150 ml) is boiled during 4 hours.

After evaporation of the solvent, the solid residue consists of 5-(2-chlorobenzyl)-thieno[3,2-c]-pyridinium chloride which melts at 166°C (derivative n° 30). This compound is taken up into a solution comprising ethanol (300 ml) and water (100 ml). Sodium borohydride ($NaBH_4$) (20 g) is added portionwise to the solution maintained at room temperature. The reaction medium is maintained under constant stirring during 12 hours and is then evaporated. The residue is taken up into water and made acidic with concentrated hydrochloric acid to destroy the excess reducing agent. The mixture is then made alkaline with ammonia and extracted with ether. The ether solution is washed with water, dried and evaporated. The oily residue is dissolved in isopropanol (50 ml) and hydrochloric acid in ethanol solution is then added thereto.

After filtration and recrystallization from ethanol, there are obtained 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine hydrochloride crystals (yield: 60%) having a melting point (Koefler block) of 190°C.

References

Merck Index 9272
DFU 1 (4) 190 (1976)
Kleeman & Engel p. 884
OCDS Vol. 3 p. 228 (1984)
DOT 15 (8) 354 (1979)
I.N. p. 951
Castaigne, A.R.J.; U.S. Patent 4,051,141; September 27, 1977; assigned to Centre d'Etudes Pour l'Industrie Pharmaceutique (France)

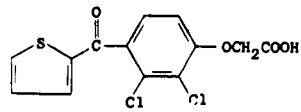
TICRYNAFEN

Therapeutic Function: Diuretic, hypertensive

Chemical Name: [2,3-Dichloro-4-(2-thienylcarbonyl)phenoxy] acetic acid

Common Name: Thienylic acid

Structural Formula:



Chemical Abstracts Registry No.: 41080-04-9

Trade Name	Manufacturer	Country	Year Introduced
Diflurex	Anphar	France	1976
Diflurex	Ritter	Switz.	1978
Selacryn	SK Dauelsberg	W. Germany	1979
Selacryn	SKF	U.S.	1979

Raw Materials

2,3-Dichloroanisole
Ethyl chloroacetate
Sulfuric acid
Thiophene-2-carboxylic acid chloride
Sodium hydroxide

Manufacturing Process

(a) To a solution of 55 g of 2,3-dichloroanisole (0.31 mol), 91 g of thiophene-2-carboxylic acid chloride (0.62 mol) and 180 ml carbon disulfide; there was added little by little 82.7 g of anhydrous aluminum chloride, keeping the temperature at about 25°C. The reaction mixture was stirred at ambient temperature for five hours, left standing overnight and then heated for one hour at 55°C. The solution was cooled and hydrolyzed by 250 g of ice and 60 ml concentrated hydrochloric acid. The precipitate formed is treated with a 30% solution of caustic soda, then washed with water. After recrystallization in 95% ethanol, 88.6 g (yield 92%) of crystals are obtained melting at 108°C.

The process can also be carried out without solvent keeping the same proportions of reactants, or in methylene chloride by adding a slight excess of aluminum chloride powder to a solution of one mol of dichloroanisole and one mol of acid chloride.

(b) 88.6 g of the ketone just obtained (0.308 mol) were dissolved in 300 ml of benzene, 123.5 g of aluminum chloride was added in small doses, and the mixture was boiled under reflux for two hours.

The reaction mixture was hydrolyzed by 500 g ice; the precipitate extracted and taken up in a 10% aqueous caustic soda solution. The benzene phase obtained after hydrolysis is concentrated. The oil obtained is treated as above and the precipitate added to the other. The crystals were recrystallized in 50% ethanol, 60 g of product were obtained, melting at 142°C.

The reaction may also be effected with excellent yields in methylene chloride.

(c) A solution of sodium ethylate was prepared by dissolving 3.45 g of sodium (0.15 mol) in 300 ml absolute ethanol. There was then added 31 g of the preceding phenol (0.15 mol) then 25.8 g ethyl chloroacetate. The mixture was refluxed for 15 hours. Hot extraction was carried out to eliminate the sodium chloride.

The ester precipitated on cooling the filtrate. The product was recrystallized once in isopropanol to give 29.4 g of crystals melting at 58°C. The pure product melts at 63°C to 64°C.

The ester was dissolved in a solution of 500 ml 95% ethanol and 9 ml of 10N caustic soda.

The mixture was boiled under reflux for 30 minutes. The precipitate of the sodium salt of the acid which forms in the cold was extracted and taken up in warm water. The free acid was then precipitated in mineral acid medium. After recrystallization in 50% ethanol, it melted at 148°C to 149°C.

References

Merck Index 9273
Kleeman & Engel p. 886
OCDS Vol. 2 p. 104 (1980)
DOT 12 (10) 413 (1976)
I.N. p. 38
Godfroid, J.J. and Thuillier, J.E.; U.S. Patent 3,758,506; September 11, 1973; assigned to Centre Europeen de Recherches Pharmacologiques (C.E.R.P.H.A.) (France)

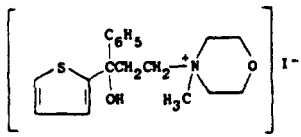
TIEMONIUM IODIDE

Therapeutic Function: Antispasmodic, anticholinergic

Chemical Name: 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl] -4-methyl-morpholinium iodide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 144-12-7

Trade Name	Manufacturer	Country	Year Introduced
Visceralgine	Riom	France	1963
Viseralgina	S.I.T.	Italy	1965
Ottimal	Farnex	Italy	–

Raw Materials

Bromobenzene
Thienyl-morpholinoethyl ketone
Magnesium
Methyl iodide

Manufacturing Process

(a) N-(3-hydroxy-3-phenyl-3-α-thienyl-propyl) morpholine was first prepared: The following quantities of reactants were mixed in a 2-liter balloon flask having 3 tubes fitted respectively with a mercury-sealed agitator, a reflux condenser having a calcium chloride seal, and a dropping funnel:

Magnesium turnings	27 g (1.1 g at. wt)
Bromobenzene	181 g (1.15 mol)
Anhydrous ether	500 cc

(b) To the cold Grignard solution was added a solution containing:

Thienyl-morpholinoethyl ketone	180 g (0.8 mol)
Anhydrous ether	250 cc

The ketone, preferably prepared by a Grignard reaction, was added in such a way as to maintain the ether under constant reflux. When all of the solution had been added, the mixture was refluxed for a further hour. The mixture was then allowed to stand for 12 hours at ambient temperature, after which the reaction mass was extracted with ice and ammonium chloride in known manner.

(c) The ether solution was treated with 2N hydrochloric acid solution and the amino-alcohol was obtained as the hydrochloride (yield approximately 60%); it was purified by recrystallization from methanol.

The resulting product was dissolved in water, made alkaline with dilute NH_4OH and was extracted with ether. After evaporation of the ether, the amino-alcohol was obtained as a base.

(d) To prepare the quaternary ammonium iodide, the amino-alcohol above was dissolved in a minimum amount of anhydrous ether and was treated with its own weight of methyl iodide. A well-crystallized product was obtained and was washed with anhydrous ether. (Melting point 189°C to 191°C).

References

Merck Index 9274
Kleeman & Engel p. 885
DOT 15 (9) 427 (1979)
I.N. p. 951
Laboratoires d'Analyses et de Recherches Biologiques Mauvernay C.E.R.F.A.; British Patent 953,386; March 25, 1964

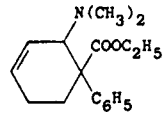
TILIDINE HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: 2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylic acid ethyl ester hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 27107-79-5; 20380-58-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Valoron	Goedecke	W. Germany	1970
Valoron	Isom	Italy	1983
Kitadol	Larma	Spain	–
Perdolat	Inca	Argentina	–
Tilitrate	Substancia	Spain	–

Raw Materials

Diethylamine
Atropic acid ethyl ester
Crotonaldehyde
Hydrogen chloride

Manufacturing Process

In a first step, dimethylamine is reacted with crotonaldehyde to give 1-(dimethylamino)-1,3-butadiene.

A solution of 194 grams (2 mols) of fresh-distilled 1-(dimethylamino)-1,3-butadiene is combined at room temperature in a 1 liter round-bottom flask with 352 grams (2 mols) atropic acid ethyl ester. After being stirred for about 10 minutes, the reaction mixture gradually becomes exothermic. By cooling with ice water, the contents of the flask are kept at a temperature of 40° to 60°C. After the reaction has ceased, the mixture is kept overnight (about 8 to 24 hours) at room temperature. The next day the viscous product is dissolved in 10 liters of ether and precipitated with ethereal hydrogen chloride forming the corresponding hydrochloride. By fractional crystallization from ethyl acetate/methyl ethyl ketone (10:1), an almost complete separation of the isomeric cis/trans isomers (I) and (II) is achieved. The separation can be carried out very easily due to the low solubility of the 1½-hydrate of (I). Therefore, during the crystallization a sufficient quantity of water for the formation of the 1½-hydrate of (I) is added to the mixture of solvents, whereby (I) readily precipitates.

Isomer (I): 4-phenyl-3-cis-dimethylamino-4-cis-carbethoxy-Δ^1-cyclohexene hydrochloride, [ethyl-cis-3-(dimethylamino)-4-phenyl-1-cyclohexene-4-carboxylate hydrochloride], MP 84°C (the free base boils at 97.5° to 98°C at 0.01 mm pressure), 64.4% yield.

Isomer (II): 4-phenyl-3-trans-dimethylamino-4-trans-carbethoxy-Δ^1-cyclohexene hydrochloride, [ethyl-trans-3-(dimethylamino)-4-phenyl-1-cyclohexene-4-carboxylate hydrochloride], MP 159°C (the free base boils at 95.5° to 96°C at 0.01 mm pressure), 22.2% yield.

References

Merck Index 9280
Kleeman & Engel p. 887
DOT 7 (1) 33 (1971)
I.N. p. 952
Satzinger, G.; U.S. Patent 3,557,127; January 19, 1971; assigned to Warner-Lambert Pharmaceutical Company

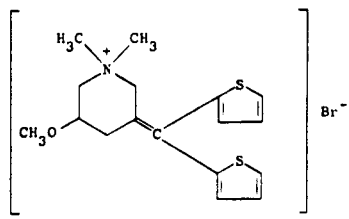
TIMEPIDIUM BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 3-(Di-2-thienylmethylene)-5-methoxy-1,1-dimethylpiperidinium bromide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 35035-05-3

Trade Name	Manufacturer	Country	Year Introduced
Sesden	Tanabe Seiyaku	Japan	1976
Mepidum	Poli	Italy	—

Raw Materials

5-Hydroxynicotinic acid
Dimethyl sulfate
2-Thienyl bromide
Methyl bromide
Methanol
Hydrogen
Hydrogen chloride

Manufacturing Process

120 g of 5-hydroxynicotinic acid are dissolved in 1 liter of methanol. After saturating with dry hydrogen chloride gas at 0°C, the solution is refluxed for 2 hours. Then, the solution is concentrated to dryness. The residue thus obtained is dissolved in water. The solution is neutralized with sodium bicarbonate. The precipitated crystals are collected by filtration, washed with water and then dried. 126 g of methyl 5-hydroxynicotinate are obtained. Yield: 93%. Melting point 184°C to 186°C.

460 g of methyl 5-hydroxynicotinate and 621 g of potassium carbonate are suspended in 200 ml of tetrahydrofuran-methanol (4:1). 1,134 g of dimethyl sulfate are added dropwise to the suspension in nitrogen atmosphere at room temperature. The mixture is stirred overnight at the same temperature and then filtered. The filtrate is concentrated to dryness. The residue thus obtained is mixed with 1.6 liters of methanol and 280 ml of Raney-nickel, and hydrogenated overnight in an autoclave at room temperature and at a pressure of 85 atmospheres. 200 g of Raney-nickel are added to the reaction mixture. The mixture is adjusted to pH 9.5 with triethylamine, and is further subjected to hydrogenation for 20 hours in an autoclave at 70°C and at a pressure of 100 atmospheres. Potassium carbonate and a small amount of ice are added to the reaction mixture to bring the pH to 11. The mixture is extracted with ether. After drying, the ether layer is filtered. The filtrate is evaporated to remove ether. The residue thus obtained is distilled under reduced pressure. 450 g of methyl N-methyl-5-methoxy-nipecotinate are obtained. Yield: 80%. Boiling point 80°C to 81°C/0.5 mm Hg.

A solution of 18 g of 2-thienyl bromide in 30 ml of tetrahydrofuran is gradually added to a mixture of 2.6 g of magnesium and 80 ml of tetrahydrofuran under stirring at 50°C. The mixture is stirred for 5 hours at room temperature until the magnesium is entirely dissolved in the solution. 6.2 g of methyl N-methyl-5-methoxy-nipecotinate are added to the mixture. Then, the mixture is refluxed for 4 hours. After the reaction is completed, tetrahydrofuran is distilled off under reduced pressure. An aqueous ammonium chloride solution is added to the residue, and the solution is extracted with chloroform. The extract is dried and then evaporated to remove chloroform. The viscous oil thus obtained is recrystallized from a mixture of benzene and ether. 7 g of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidyl)-carbinol are obtained as crystals. Melting point 142°C to 146°C.

7 g of the product are dissolved in 150 ml of 10% hydrochloric acid, and the solution is heated at 80°C for 30 minutes. After the reaction is completed, the solution is basified with sodium hydroxide and then extracted with ether. The extract is washed with water, dried and evaporated to remove ether. 5 g of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidylidene)-methane are obtained as pale yellow oil.

365 mg of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidylidene)-methane are dissolved in 15 ml of ether. 1 ml of methyl bromide is added to the solution. Then, the solution is stirred overnight. The precipitated crystals are collected by filtration and recrystallized from a mixture of acetone and ether. 390 mg of di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidylidene)-methane methyl bromide are obtained as colorless crystals. Melting point 198°C to 200°C.

References

Merck Index 9283
Kleeman & Engel p. 888
DOT 12 (12) 490 (1976)
I.N. p. 952
Kawazu, M., Kanno, T., Saito, S. and Tamaki, H.; *U.S. Patent 3,764,607; October 9, 1973;* assigned to Tanabe Seiyaku Co., Ltd. (Japan)

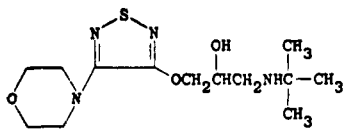
TIMOLOL MALEATE

Therapeutic Function: Antiarrhythmic, antiglaucoma

Chemical Name: S-(−)-1-tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 26921-17-5; 26839-75-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Blocadren	MSD	U.K.	1974
Timacor	MSD	France	1976
Timserin	Sharp & Dohme	W. Germany	1976
Timoptic	MSD	U.S.	1978
Timoptic	Chibret	Switz.	1978
Timoptol	MSD	U.K.	1979
Timoptol	Sharp & Dohme	W. Germany	1979
Blocadren	MSD	Italy	1980
Timoptic	MSD	Italy	1980
Timoptol	Merck Banyu	Japan	1981
Blocadren	MSD	U.S.	1981
Betim	Leo	Denmark	–
Cardina	Orion	Finland	–
Chibro-Timoptol	Chibret	France	–
Cusimolol	Cusi	Spain	–

Raw Materials

Bromoacetol
p-Toluene sulfonyl chloride
3-Morpholino-4-hydroxy-1,2,5-thiadiazole
t-Butylamine
Sodium borohydride
Maleic acid

Manufacturing Process

Step A: Preparation of 3-tert-Butylamino-2-Oxopropanol – To an aqueous solution of tert-butylamine (1 mol) at ambient temperature, there is added slowly and with vigorous stirring 2 mols bromoacetol. The reaction mixture is allowed to stand at ambient temperature for about 5 hours whereupon it is made basic by the addition of sodium hydroxide.

The reaction mixture then is extracted with ether, the excess amine is removed from the ethereal solution under reduced pressure and the ether then removed by evaporation to give 3-tert-butylamino-2-oxopropanol.

Step B: A solution of the 3-tert-butylamino-2-oxopropanol in a mixture of pyridine hydrochloride and pyridine is treated with p-toluenesulfonylchloride. The mixture is stirred for ½ hour at 25° to 30°C and then poured into cold water. The solution is treated with potassium carbonate and the pyridine evaporated in vacuo at a temperature between 55° and 60°C. The aqueous residue is treated with potassium carbonate and the mixture extracted with methylene chloride. Evaporation of the dried extract provides 1-toluenesulfonyloxy-2-oxo-3-tert-butylaminopropane.

Step C: Preparation of 3-Morpholino-4-(3-tert-Butylamino-2-Oxopropoxy)-1,2,5-Thiadiazole – The 1-toluenesulfonyloxy-2-oxo-3-tert-butylaminopropane, prepared as described in Step B, (11 mols) is added to 0.80 N methanolic sodium methoxide (15 ml) at 0°C. The mixture is stirred for 15 minutes at 0° to 5°C, treated with 3-morpholino-4-hydroxy-1,2,5-thiadiazole (4.29 grams) and then refluxed for 16 hours. The solvent is evaporated in vacuo and the residue is treated with excess potassium carbonate to provide 3-morpholino-4-(3-butylamino-2-oxopropoxy)-1,2,5-thiadiazole.

Step D: Chemical Reduction Preparation of 3-Morpholino-4-(3-tert-Butylamino-2-Hydroxypropoxy)-1,2,5-Thiadiazole – The 3-morpholino-4-(3-tert-butylamino-2-oxopropoxy)-1,2,5-thiadiazole (0.01 mol) is dissolved in isopropanol (10 ml). To the solution is added sodium borohydride in portions until the initial evolution of heat and gas subsides. The excess sodium borohydride is destroyed by addition of concentrated hydrochloric acid until the mixture remains acidic. The precipitate of sodium chloride is removed, ether is added, and the solution is concentrated to crystallization. The solid material is removed by filtration and dried thus providing 3-morpholino-4-(3-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, MP 161° to 163°C (as hydrochloride).

Alternative Step D: Reduction with a Reductate – Sucrose (1 kg) is dissolved in water (9 liters) in a 20-liter bottle equipped with a gas trap. Baker's yeast (*Saccharomyces cerevisiae*, 1 kg) is made into a paste with water (1 liter) and added to the sucrose solution with stirring. After lively evolution of gas begins (within 1 to 3 hours), 3-morpholino-4-(3-tert-butylamino-2-oxopropoxy)-1,2,5-thiadiazole hydrogen maleate [1.35 mols, prepared by reaction of the 3-morpholino-4-(3-tert-butylamino-2-oxopropoxy)-1,2,5-thiadiazole with an equimolar quantity of maleic acid in tetrahydrofuran]. The mixture is allowed to stand until fermentation subsides, after which the bottle is kept in a 32°C incubator until all fermentation has ended (in approximately 1 to 3 days). The yeast is filtered off with addition of diatomaceous earth and the filtrate is evaporated to dryness to give S-3-morpholino-4β-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, MP 195° to 198°C (as hydrogen maleate), according to U.S. Patent 3,619,370.

Step E: The base may be converted to the maleate by maleic acid.

References

Merck Index 9284
Kleeman & Engel p. 889
PDR pp. 1145, 1211, 1214
OCDS Vol. 2 p. 272 (1980)
DOT 10 (4) 145 (1974) & 16 (3) 92 (1980)
I.N. p. 953
REM p. 907
Weinstock, L.M., Tull, R.J. and Mulvey, M.D.; U.S. Patent 3,619,370; November 9, 1971; assigned to Charles E. Frosst & Co.
Wasson, B.K.; U.S. Patent 3,655,663; April 11, 1972
Weinstock, L.M., Tull, R.J. and Mulvey, D.M.; U.S. Patent 3,657,237; April 18, 1972; assigned to Charles E. Frosst & Co.

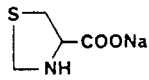
TIMONACIC SODIUM

Therapeutic Function: Hepatotherapeutic, choleretic

Chemical Name: 4-Thiazolidinecarboxylic acid sodium salt

Common Name: ATC

Structural Formula:



Chemical Abstracts Registry No.: 444-27-9 (acid)

Trade Name	Manufacturer	Country	Year Introduced
Hepaldine	Riker	France	1964
Leberschutz	Karner	W. Germany	1977
Dexotepa	Ayerst	Italy	1979
Tiazolidin	U.C.M.-Difme	Italy	1980
Heparegene	Syntex-Pharm.	Switz.	–
Thiobiline	Riker	France	–

Raw Materials

Cysteine
Formaldehyde
Sodium hydroxide

Manufacturing Process

Cysteine is first dissolved in distilled water which has been freed of oxygen by boiling. Formaldehyde of 30% (w/v) concentration is added while stirring and the temperature of the mixture rises, while the thiazolidine carboxylic acid begins crystallizing. The stirring is continued for 2 hours after which ethyl alcohol of 95% (w/v) concentration is added to induce further crystallization. The mixture is left to stand for 24 hours at 4°C. The mixture is then filtered with retention of a crude product, which is purified by recrystallization from boiling distilled water. The crystals are then dried at about 40°C. The free acid is then converted to the sodium salt with NaOH.

References

Merck Index 9285
DFU 5 (8) 415 (1980)
Kleeman & Engel p. 890
I.N. p. 953
Sogespar, S.A.; British Patent 1,041,787; September 7, 1966

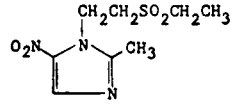
TINIDAZOLE

Therapeutic Function: Antitrichomonal (vaginal)

Chemical Name: 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 19387-91-8

Trade Name	Manufacturer	Country	Year Introduced
Simplotan	Pfizer	W. Germany	1971
Fasigyne	Pfizer	France	1975
Fasigyn	Pfizer	Italy	1975
Fasigyn	Pfizer Taito	Japan	1981
Fasigyn	Pfizer Taito	U.K.	1982
Amplium	Farmasa	Brazil	–
Pletil	Andromaco	Brazil	–
Protocide	Unipharm	Israel	–
Sorquetan	Basotherm	W. Germany	–
Tinigyn	Leiras	Finland	–
Tricanix	Orion	Finland	–
Trichogin	Chiese	Italy	–
Trimonase	Tosi	Italy	–

Raw Materials

Ethyl sulfonyl ethanol
p-Toluenesulfonyl chloride
2-Methyl-5-nitroimidazole

Manufacturing Process

The preparation of ethylsulfonylethyl-p-toluenesulfonate is carried out in the following manner: 69.0 grams (0.5 mol) ethylsulfonylethanol dissolved in 150 ml pyridine is cooled to 0°C with stirring and while maintaining the temperature between 0° to 10°C, 95 grams (0.5 mol) p-toluenesulfonyl chloride is added in portions over a 10 minute period. After this time, 250 ml water is added slowly and the mixture extracted with chloroform, the organic phase washed first with 2 N HCl, then with water, separated and dried. The product which crystallizes on cooling is filtered and dried to give 77.5% yield of this intermediate.

A mixture of 12.7 grams (0.1 mol) of 2-methyl-5-nitroimidazole and 58.4 grams (0.2 mol) ethylsulfonylethyl-p-toluenesulfonate is heated with stirring, under nitrogen, at 145° to 150°C for about 4 hours. After this time, the reaction mixture is extracted with 500 ml hot water, the aqueous portion adjusted with 10% Na_2CO_3 to a pH of 9 and extracted with chloroform (3 times with 150 ml portions). The separated organic phase is washed with water, dried with Na_2SO_4 and evaporated to dryness. The crude tinidazole product is then crystallized from benzene to give 4.36 grams of product having a MP of 127° to 128°C.

References

Merck Index 9287
Kleeman & Engel p. 890
DOT 7 (5) 193 (1971) & 8 (2) 73 (1972)
I.N. p. 953
REM p. 1224
Butler, K.; U.S. Patent 3,376,311; April 2, 1968; assigned to Chas. Pfizer & Co., Inc.

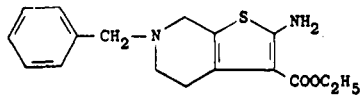
TINORIDINE

Therapeutic Function: Antiinflammatory

Chemical Name: 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c] pyridine-3-carboxylic acid ethyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 24237-54-5; 23237-55-6 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Nonflamin	Yoshitomi	Japan	1971
Dimaten	Promeco	Argentina	–

Raw Materials

1-Benzyl-4-piperidone
Sulfur
Ethyl cyanoacetate
Morpholine

Manufacturing Process

A solution of 1-benzyl-4-piperidone, ethyl cyanoacetate, powdery sulfur and morpholine in ethanol is heated moderately under reflux for about 20 minutes to dissolve the powdery sulfur. The mixture is heated under reflux for one further hour to complete the reaction. On standing at room temperature, the mixture yields a precipitate. The precipitate is collected by filtration, washed well with methanol and recrystallized from methanol to give 2-amino-6-benzyl-3-ethoxycarbonyl-4,5,6,7-tetrahydrothieno(2,3-c)-pyridine as almost colorless needles melting at 112° to 113°C.

References

Merck Index 9289
Kleeman & Engel p. 891
DOT 7 (6) 224 (1971)
I.N. p. 954
Nakanishi, M., Tahara, T., Imamura, H. and Maruyama, Y.; U.S. Patent 3,563,997; Feb. 16, 1971; assigned to Yoshitomi Pharmaceutical Industries, Ltd., Japan

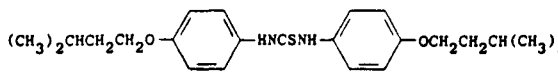
TIOCARLIDE

Therapeutic Function: Antitubercular

Chemical Name: N,N'-[4-(3-Methylbutoxy)phenyl] thiourea

Common Name: Thiocarlide

Structural Formula:



Chemical Abstracts Registry No.: 910-86-1

Trade Name	Manufacturer	Country	Year Introduced
Tiocarlide	Ciba	W. Germany	1963
Tiocarlide	Ciba	Italy	1964
Tiocarlide	Ciba	France	1965
Isoxyl	Continental Pharm	U.K.	1969
Amixyl	Inibsa	Portugal	—
Disoxyl	Ferrosan	Denmark	—

Raw Materials

Isoamyloxyaniline
Carbon disulfide

Manufacturing Process

100 parts by weight of p-isoamyloxyaniline are refluxed for 6 hours with 34 parts by volume of carbon disulfide, 300 parts by volume of ethanol and 5 parts by weight of potassium ethyl xanthate. The reaction mixture is then cooled and the formed 1,3-bis-(p-isoamyloxyphenyl)-2-thiourea is filtered off, washed with a small amount of ethanol and water, and recrystallized from ethanol. The thus-obtained product melts at 134°C to 145°C.

References

Merck Index 9292
Kleeman & Engel p. 891
I.N. p. 954
Huebner, C.F. and Scholz, C.R.; U.S. Patent 2,703,815; March 8, 1955; assigned to Ciba Pharmaceutical Products, Inc.

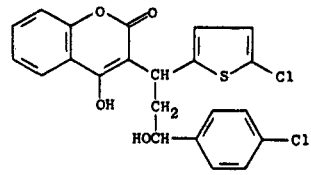
TIOCLOMAROL

Therapeutic Function: Anticoagulant

Chemical Name: 3-[3-(4-Chlorophenyl)-1-(5-chloro-2-thienyl)-3-hydroxypropyl]-4-hydroxy-2H-1-benzopyran-2-one

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 22619-35-8

Trade Name	Manufacturer	Country	Year Introduced
Apegmone	Oberval	France	1978

Raw Materials

p-Chloroacetophenone
4-Hydroxycoumarin
5-Chlorothiophene-2-aldehyde
Aluminum isopropylate

Manufacturing Process

(a) 1-parachlorophenyl-3-(5'-chloro-2'-thienyl)-2-propen-1-one – *(a)* This new compound was prepared in the following manner:

4.4 g of NaOH, in solution in 40 ml of water and 20 ml of ethanol, are cooled to 120°C, and then there are successively added at this temperature 13.2 g (0.086 mol) of parachloroacetophenone and 12.6 g of 5-chlorothiophene-2-aldehyde. The solution is left standing for 3 hours while stirring at ambient temperature and the precipitate which has formed is centrifuged off, whereafter it is washed with water and recrystallized from alcohol. Yield: 18.4 g, i.e., 75.7% of product, melting at 134°C.

(b) The ketone prepared according to *a* is condensed at the rate of 14.15 g (0.05 mol) with 8.9 g (0.055 mol) of 4-hydroxycoumarin in 80 ml of water in the presence of 42 mg of hexamethyleneimine. Heating takes place for 4 hours under reflux and, after recrystallization, first of all from a mixture of acetone and water and then from benzene, there are obtained: 12.6 g of 3-(4'-hydroxy-3'-coumarinyl)-3-(5''-chloro-2''-thienyl)-parachloropropiophenone, melting at 162°C (sealed tube).

(b) 4.45 g (0.01 mol) of 3-(4'-hydroxy-3'-coumarinyl)-3-(5''-chloro-2''-thienyl)-parachloropropiophenone, in solution in 75 ml of isopropanol, are reduced with 6.12 g (0.03 mol) of aluminum isopropylate, introduced while stirring and in small quantities at ambient temperature.

The solution is refluxed for one hour and after cooling it is poured into 250 ml of ice and 15 ml of concentrated HCl. On standing, a white precipitate is obtained, which is centrifuged, washed with water, taken up in methanol and filtered.

5 volumes of water are added to this solution, and it is allowed to crystallize at ambient temperature.

The product is analytically pure and shows a pasty fusion at 104°C (sealed tube). Yield: 89%.

References

Merck Index 9293
Kleeman & Engel p. 892
DOT 14 (8) 383 (1978)
I.N. p. 954
Boschetti, E., Molho, D. and Fontaine, L.; U.S. Patent 3,574,234; April 6, 1971; assigned to Lyonnaise Industrielle Pharmaceutique (LIPHA) (France)

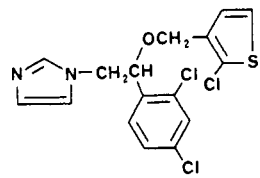
TIOCONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1-[2-[(2-Chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 65899-73-2

Trade Name	Manufacturer	Country	Year Introduced
Fungata	Pfizer	W. Germany	1981
Trosyd	Pfizer	Switz.	1983
Trosyd	Pfizer	U.S.	1983

Raw Materials

1-(2,4-Dichlorophenyl)-2-(1-imidazolyl)ethanol
Sodium hydride
2-Chloro-3-chloromethylthiophene

Manufacturing Process

A solution of 1-(2,4-dichlorophenyl)-2-(1-imidazolyl)ethanol (1.5 g, 5.8 mmol) dissolved in dry tetrahydrofuran (10 ml) was added to a stirred suspension of sodium hydride (0.39 g, as 80% dispersion in oil, 16 mmol) in dry tetrahydrofuran (10 ml) and warmed to 70°C for 90 minutes.

The mixture was cooled in ice and a solution of 2-chloro-3-chloromethylthiophene (8.8 mmol) in dry tetrahydrofuran was added. The mixture was heated at 70°C for 3 hours and allowed to stir at room temperature overnight. The solvent was removed under vacuum and the residue stirred with dry ether (200 ml). The ether solution was filtered through Celite and saturated with hydrogen chloride gas to precipitate an oil which was solidified by trituration with ether and ethyl acetate. The solid product was collected and recrystallized from a mixture of acetone and diisopropyl ether to give the product, melting point 168°C to 170°C.

References

Merck Index 9294
DFU 5 (10) 509 (1980)
DOT 19 (8) 341 (1983)
I.N. p. 954
REM p. 1231
Gymer, G.E.; U.S. Patent 4,062,966; December 13, 1977; assigned to Pfizer, Inc.

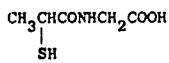
TIOPRONIN

Therapeutic Function: Antidote in heavy metal poisoning

Chemical Name: N-(2-Mercapto-1-oxopropyl)glycine

Common Name: Mercamidum

Structural Formula:



Chemical Abstracts Registry No.: 1953-02-2

Trade Name	Manufacturer	Country	Year Introduced
Thiosol	Coop. Farm.	Italy	1969
Mercaptopropionylglycin	Fresenius	W. Germany	1976
Mucolysin	Proter	Italy	1976
Mucolysin	Interdecta	Switz.	1982

Trade Name	Manufacturer	Country	Year Introduced
Capen	Phoenix	Argentina	–
Epatiol	Medici	Italy	–
Sutilan	Cusi	Spain	–
Thiola	Santen	Japan	–
Vincol	Reig. Jofre	Spain	–

Raw Materials

α-Mercaptopropionic acid
Thionyl chloride
Sodium
Benzyl chloride
Glycine
Ammonia

Manufacturing Process

α-Benzylmercaptopropionic acid (melting point 76°C to 78°C; 100 g) prepared by condensation of α-mercaptopropionic acid with benzyl chloride is allowed to stand overnight with 80 g of thionyl chloride. After removal of excess thionyl chloride distillation in vacuo gives 70 g of α-benzylmercaptopropionic acid chloride of boiling point 138°C to 139°C/7 to 8 mm Hg.

Then, 25 g of glycine is dissolved in 165 ml of 2N sodium hydroxide solution and 70 g of α-benzylmercaptopropionic acid chloride and 100 ml of 2N sodium hydroxide solution are dropped thereinto simultaneously at 3°C to 5°C. The solution is then stirred at room temperature for 3 to 4 hours to complete the reaction, the reaction solution is washed with ether, the aqueous layer is acidified with hydrochloric acid, and the resulting crystals are collected by filtration. These are recrystallized from a mixture of methanol and ethyl acetate to give 60 g of α-benzylmercaptopropionylglycine of melting point 133°C to 134°C.

This α-benzylmercaptopropionylglycine (60 g) is dissolved in 400 ml of liquid ammonia, kept at about -50°C, and 12 g of sodium metal is gradually added thereto. After the reaction, excess ammonia is removed therefrom, the residue is dissolved in water, washed with ether and the residual aqueous layer is adjusted to pH 1 with hydrochloric acid and concentrated in vacuo in a stream of hydrogen sulfide. The crystalline residue is dried and recrystallized from ethyl acetate to give 25 g of α-mercaptopropionylglycine of melting point 95°C to 97°C.

References

Merck Index 9296
Kleeman & Engel p. 893
DOT 14 (1) 38 (1978)
I.N. p. 955
Mita, I., Toshioka, N. and Yamamoto, S.; U.S. Patent 3,246,025; April 12, 1966; assigned to Santen Pharmaceutical Co. (Japan)

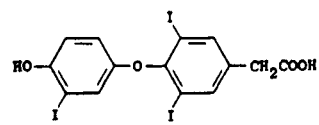
TIRATRICOL

Therapeutic Function: Thyroid replacement therapy

Chemical Name: [4-(4-Hydroxy-3-iodophenoxy)-3,5-diiodophenyl] acetic acid

Common Name: Triiodothyroacetic acid

Structural Formula:



Chemical Abstracts Registry No.: 51-24-1

Trade Name	Manufacturer	Country	Year Introduced
Triacana	Ana	Italy	1972

Raw Materials

Ethyl-3,5-diiodo-4-(4'-hydroxyphenoxy)phenyl acetate
Hydriodic acid
Iodine

Manufacturing Process

Preparation of 3:5-diiodo-4-(4'-hydroxyphenoxy)phenylacetic acid (diac): A solution of ethyl 3:5-diiodo-4-(4'-methoxyphenoxy)phenyl acetate (9.5 g) in acetic acid (60 ml) was heated under reflux with hydriodic acid (SG 1.7, 50 ml) and red phosphorus (0.5 g) for 1 hour. The hot solution was filtered and the filtrate concentrated at 50°C and 15 mm of mercury to above 20 ml. The residue was treated with water (70 ml) containing a little sodium thiosulfate to decolorize the product. The solid was collected by filtration and purified by the method of Harington and Pitt-Rivers [*Biochem. J.* (1952), Vol. 50, page 438]. Yield 8.36 g (95%). After crystallization from 70% (v/v) acetic acid it melted at 219°C.

A solution of 438 mg of diac in methanol (20 ml) and ammonia solution (SG 0.88; 20 ml) was iodinated at 0°C with 1.8 ml 1 N iodine solution. The product was isolated in almost theoretical yield in a manner similar to that described for tetrac. After crystallization from 50% (v/v) methanol, triac was obtained as colorless needles which melted over the range 65°C to 90°C according to the rate of heating. The molten form resolidified at about 110°C and finally melted at 180°C to 181°C without decomposition. The compound, dried at 25°C/3 mm over silica gel, contains methanol of crystallization.

References

Merck Index 9299
I.N. p. 956
Wilkinson, J.H.; British Patent 805,761; December 10, 1958; assigned to National Research Development Corp. (U.K.)

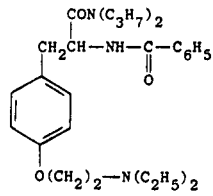
TIROPRAMIDE

Therapeutic Function: Smooth muscle relaxant

Chemical Name: α-(Benzoylamino)-4-[2-(diethylamino)ethoxy]-N,N-dipropylbenzenepropanamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 55837-29-1

Trade Name	Manufacturer	Country	Year Introduced
Maiorad	Rotta	Italy	1982
Alfospas	Rorer	U.S.	–

Raw Materials

N-Benzoyl-DL-tyrosil-di-n-propylamide
Sodium methylate
2-Diethylaminoethyl chloride

Manufacturing Process

36.8 g (0.1 mol) of N-benzoyl-DL-tyrosil-di-n-propylamide are suspended in 350 cc of toluene; there are then added, under agitation, 5.4 g (0.1 mol) of sodium methylate and 50 cc (0.1 mol) of a titrated toluenic solution of 2-diethylamino-ethyl-chloride. The temperature is taken up to 105°C and the solution is left at this temperature, in agitation, for 12 hours. The toluenic solution is extracted with HCl 2N; the aqueous acid phase is alkalized, cold, with sodium carbonate, and then reextracted with successive portions of ethyl acetate.

The reunited organic phases are anhydrified upon anhydrous Na_2SO_4, filtered and dried off. The oily residue which is obtained crumbles after a few hours of rest. Amount obtained 39.2 g. Yield 84%. Melting point 65°C to 67°C (crystallizes with petroleum ether).

The free base can be salified so as to render it hydrosoluble. For this purpose, for example, it is dissolved in acetone and precipitated as an oxalate by the addition of a solution of oxalic acid in ethanol. Recrystallizes with ethanol. Melting point (oxalate): 159°C to 162°C. Alternatively it can be dissolved in acetone and precipitated with an acetone solution of HCl. Recrystallizes with acetone-ethanol. Melting point (chlorhydrated): 181°C to 183°C.

References

Merck Index 9301
DFU 7 (6) 413 (1982)
DOT 19 (2) 114 & (5) 271 (1983)
I.N. p. 956
Makovec, F., Rovati, L. and Senin, P.; U.S. Patent 4,004,008; January 18, 1977; assigned to Rotta Research Laboratorium S.p.A. (Italy)

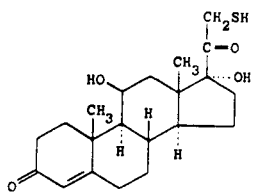
TIXOCORTOL PIVALATE

Therapeutic Function: Antiinflammatory

Chemical Name: 11,17-Dihydroxy-21-mercaptopregn-4-ene-3,20-dione

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 55560-96-8; 61951-99-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Pivalone	Jouveinal	France	1978

Raw Materials

S-Thiopivalic acid
Sodium methylate
Dihydroxy-11β,17α-iodo-21-dioxo-3,20-pregnene-4

Manufacturing Process

In a reactor of 50 liters, sodium S-thiopivalate is prepared from 100 g of S-thiopivalic acid (0.844 mol), 214 cc of solution of sodium methylate, 3.95M (0.844 mol) in 25 liters of anhydrous acetone.

There are then added 285 g (0.603 mol) of dihydroxy-11β,17α-iodo-21-dioxo-3,20-pregnene-4 and the mixture is brought up to the acetone reflux for two hours. The solvent is eliminated by distillation under vacuum until there is obtained a syrupy residue which is poured into 10 liters of iced water. The insoluble part is filtered and dried under vacuum.

The crude product is purified by recrystallization from ethanol; weight: 250 g; yield: 89.5%.

References

Merck Index 9315
Kleeman & Engel p. 895
I.N. p. 957
Torossian, D.R., Aubard, G.G. and Legeai, J.M.G.; U.S. Patent 4,014,909; March 29, 1971; assigned to Jouveinal S.A. (France)

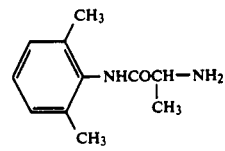
TOCAINIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: 2-Amino-2',6'-propionoxylidide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 41708-72-0

Trade Name	Manufacturer	Country	Year Introduced
Tonocard	Astra	U.K.	1981
Xylotocan	Astra	W. Germany	1982
Tonocard	Hassle	Sweden	1983
Tonocard	Astra	Australia	1983

Raw Materials

2-Bromo-2',6'-propionoxylidide
Ammonia

Manufacturing Process

The compound 2-amino-2',6'-propionoxylidide was synthesized by saturating with gaseous ammonia at room temperature a suspension of 50 g (0.195 mol) of 2-bromo-2',6'-propionoxylidide in a mixture of 500 ml of 95% alcohol and 400 ml of concentrated aqueous ammonia. The saturation was carried out under mechanical stirring. After 25 hours the mixture was resaturated with ammonia gas. The stirring at room temperature was continued for a total period of 116 hours, and a sample was taken at that time. Gas chromatographic analysis indicated that about 95% of the bromo compound had been converted to the desired product.

The solvents were evaporated in vacuo, and the residue was taken up in 80 ml of 3M hydrochloric acid. After addition of 220 ml of water, the insoluble material was filtered off, washed with 100 ml of water and then dried. The insoluble material weighed 9.5 g and was mainly unreacted bromo compound. The filtrate was reacted with 50 ml of 7M NaOH, extracted three times with methylene chloride (50 ml + 2 x 25 ml portions), dried over potassium carbonate, and then evaporated. The yield of residue was 26.8 g which corresponds to 71.4% of the theoretical yield. This residue was a colorless solidifying oil and was dissolved in 200 ml chloroform. Hydrogen chloride was bubbled in until a sample of the solution tested acidic to wet pH indicator paper. A precipitate was obtained and recovered by filtration. The precipitate was washed with chloroform and dried. The melting point was determined to be from 246°C to 247.5°C.

References

Merck Index 9319
DFU 2 (2) 141 (1977)
PDR p. 1216
OCDS Vol. 3 p. 55 (1984)
DOT 18 (3) 153 & (10) 548 (1982)
I.N. p. 958
REM p. 861
Boyes, R.N., Duce, B.R., Smith, E.R. and Byrnes, E.W.; U.S. Patents 4,218,477; August 19, 1980; and 4,237,068; December 2, 1980; both assigned to Astra Pharmaceutical Products, Inc.

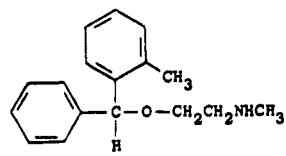
TOFENACIN HYDROCHLORIDE

Therapeutic Function: Psychostimulant

Chemical Name: N-methyl-2-[(2-methylphenyl)phenylmethoxy] ethanamine hydrochloride

Common Name: N-demethylorphenadrine hydrochloride; N-methyl-2[α-(2-tolybenzyl)oxy]-ethylamine hydrochloride

Structural Formula:



(base)

Chemical Abstracts Registry No.: 10488-36-5; 15301-93-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Elamol	Brocades	U.K.	1971
Tofalin	Brocades	Italy	1981

Raw Materials

2-Methylbenzhydrol
Methylamine
β-Chloroethanol
Hydrogen chloride

Manufacturing Process

A mixture of 39.5 grams of 2-methylbenzhydrol, 200 ml of beta-chloroethanol and 10 ml of concentrated hydrochloric acid is boiled under reflux for 4 hours. After cooling, the reaction mixture is poured into water and extracted with petroleum ether (boiling range 40° to 60°C). The layers are separated and the ethereal solution dried with sodium sulfate. It is then filtered. The filtrate is concentrated by evaporation of the solvent. The residue is distilled under reduced pressure to give 51.0 grams (yield 98%) of beta-chloroethyl-2-methylbenzhydryl ether, boiling at 156° to 158°C/2.5 mm.

A mixture of 51 grams of beta-chloroethyl-2-methylbenzhydryl ether and 35 grams of methylamine in 140 ml of methanol is heated for 6 hours in a closed vessel at a temperature of 125° to 135°C. After cooling, the reaction mixture is poured into water and extracted with petroleum ether (boiling range 40° to 60°C). The ether layer is separated and washed with a 2 N hydrochloric acid solution. The acidic layer is made alkaline and extracted with ether. The ethereal solution is separated and dried with sodium sulfate. After filtration, the solvent is evaporated and the residue distilled under reduced pressure. There is thus obtained 40 grams (yield 80%) of N-methylaminoethyl-2-methylbenzhydryl ether boiling at 139° to 143°C/0.7 mm.

The base is dissolved in anhydrous ether, and an ethereal solution of hydrochloric acid is added to form the hydrochloride of N-methylaminoethyl-2-methylbenzhydryl ether. The salt is crystallized from a mixture of ethanol and ether. Yield is 36 grams (78%); melting point 147° to 148°C.

References

Merck Index 9331
Kleeman & Engel p. 899
OCDS Vol. 2 p. 32 (1980)
DOT 8 (5) 189 (1972)
I.N. p. 960
Harms, A.F.; U.S. Patent 3,407,258; October 22, 1968; assigned to Brocades-Stheeman & Pharmacia, Netherlands

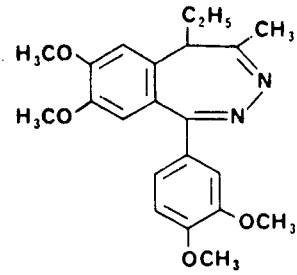
TOFISOPAM

Therapeutic Function: Tranquilizer

Chemical Name: 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzdiazepine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 22345-47-7

Trade Name	Manufacturer	Country	Year Introduced
Grandaxine	Ozothine	France	1975
Seriel	Fabre	France	–
Tavor	Gerardo Ramon	Argentina	–

Raw Materials

3,4,3',4'-Tetramethoxy-6-(α-acetopropyl)benzophenone
Hydrazine hydrate

Manufacturing Process

A mixture of 38.6 g (0.1 mol) of 3,4,3',4'-tetramethoxy-6-(α-acetopropyl)-benzophenone, 5.5 g (0.11 mol) of 100% hydrazine hydrate or 3.52 g (0.11 mol) of hydrazine, and 500 ml of absolute ethanol is boiled for 5 hours. After adding 100 ml of benzene, 400 ml of solvent mixture is distilled off from the reaction mixture by slow boiling for 3 hours. After cooling for 8 hours, 19 g of 5H-2,3-benzodiazepine derivative are separated from the residue as small, white crystals. The melting point is 133°C to 136°C (after recrystallizing from absolute ethanol, 136°C).

References

Merck Index 9332
Kleeman & Engel p. 899
DOT 9 (6) 240 (1973); 11 (5) 198 (1975) & 12 (2) 60 (1976)
I.N. p. 960
Egyesult Gyogszer és Tapszer Gyar; British Patent 1,202,579; August 19, 1970
Korosi, J., Lang, T., Komlos, E. and Erdelyi, L.; U.S. Patent 3,736,315; May 29, 1973; assigned to Egyesult Gyogszer és Tapszer Gyar (Hungary)

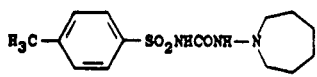
TOLAZAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[[(hexahydro-1H-azepin-1-yl)amino] carbonyl] -4-methylbenzenesulfonamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1156-19-0

Trade Name	Manufacturer	Country	Year Introduced
Tolinase	Upjohn	Italy	1964
Tolanase	Upjohn	U.K.	1965
Norglycin	Upjohn	W. Germany	1966
Tolinase	Upjohn	U.S.	1966
Diabewas	Wassermann	Italy	—
Diabutos	Medica	Finland	—
Tolazamide	Schein	U.S.	—

Raw Materials

Hexamethyleneimine
4-Methylbenzenesulfonylurethane
Sodium nitrite
Lithium aluminum hydride

Manufacturing Process

1-Nitrosohexamethyleneimine: A solution of 89.5 grams of hexamethyleneimine, 75 ml of concentrated hydrochloric acid and 36 ml of water was heated to 70°C on a steam bath. The solution was made acidic by adding 5 ml of 2 N hydrochloric acid. While maintaining the reaction mixture at 70° to 75°C, a solution of 67 grams of sodium nitrite in 95 ml of water was added with stirring over a period of 1 hour. The mixture was then stirred at 70°C for 2 hours, and then cooled. The upper oily layer was separated and the aqueous layer was then extracted with ether. The combined ether extract and oil was dried over anhydrous magnesium sulfate and concentrated to dryness. Upon distillation of the residue there was obtained 1-nitrosohexamethyleneimine as a yellow oil, boiling at 136° to 138°C/34 mm.

1-Aminohexamethyleneimine: To a mixture of 15.18 grams of lithium aluminum hydride and 400 ml of anhydrous ether was added about 10% of a solution of 51.27 grams of 1-nitrosohexamethyleneimine in 100 ml of anhydrous ether. The mixture was refluxed until the reaction started. The remainder of the solution was added at such a rate as to maintain gentle reflux. Refluxing was continued for 2 hours more, followed by the successive addition of 16 ml of water, 12 ml of 20% aqueous sodium hydroxide solution and 56 ml of water. The inorganic precipitate was removed by filtration and washed with ether. The filtrate and ether washes were dried and the ether was removed by evaporation. Upon distillation of the residue there was obtained 25.46 grams (56%) of 1-aminohexamethyleneimine as a colorless liquid boiling at 94° to 96°C/55 mm.

N-(4-Methylbenzenesulfonyl)-N'-Hexamethyleneiminourea Free Base: A mixture of 11.42 grams of 1-aminohexamethyleneimine and 24.33 grams of 4-methylbenzenesulfonylurethane was heated at 130°C (oil-bath temperature) for 2 hours. The resulting ethanol and unreacted amine were removed at 15 mm pressure for 2 hours while keeping the oil bath at 130°C. The residue was cooled and recrystallized from methanol, giving 16.73 grams (54%) of N-(4-methylbenzenesulfonyl)-N'-hexamethyleneiminourea free base melting at 163° to 166°C. After a second recrystallization from methanol, the melting point was 163.5° to 166.5°C.

References

Merck Index 9334
Kleeman & Engel p. 900
PDR pp. 1606, 1862, 1999
OCDS Vol. 1 p. 137 (1977)
DOT 3 (2) 71 (1967)
I.N. p. 960
REM p. 977
Wright, J.B.; U.S. Patent 3,063,903; November 13, 1962; assigned to The Upjohn Company

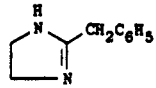
TOLAZOLINE

Therapeutic Function: Peripheral vasodilator

Chemical Name: 4,5-dihydro-2-(phenylmethyl)-1H-imidazole

Common Name: Benzazoline; 2-benzyl-4,5-imidazoline

Structural Formula:



Chemical Abstracts Registry No.: 59-98-3; 59-97-2 (Hydrochloride)

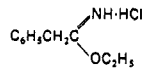
Trade Name	Manufacturer	Country	Year Introduced
Priscoline	Ciba	U.S.	1948
Tolavad	Blue Line	U.S.	1962
Benzimidon	Donau-Pharm.	Austria	–
Benzolin	Nissin	Japan	–
Dilatol	A.F.Z.	Norway	–
Dilazol	Phyteia	Switz.	–
Imidalin	Yamanouchi	Japan	–
Lambral	Maggioni	Italy	–
Priscol	Ciba	U.K.	–
Vaso-Dilatan	Agepha	Austria	–
Zoline	Protea	Australia	–

Raw Materials

Benzyl cyanide
Ethanol
Ethylenediamine

Manufacturing Process

The phenyl-acetiminoether hydrochloride of the formula



from 12 parts of benzylcyanide and ethanol and HCl is mixed with 8 parts of ethylenediamine hydrate which has been diluted with little alcohol, whereby the crystals go into solution. The whole is then heated on the water-bath until the ammonia odor has disappeared, cooled, concentrated caustic potash solution added, and the separated oil extracted with ether. The solution is dried with potassium carbonate and potassium hydroxide. After evaporation a pale oil is left which distills at 147°C under a pressure of 9 mm and which solidifies in the condenser to a white crystalline mass. The yield amounts to 90% of the theory. The hydrochloride melts at 168° to 170°C.

References

Merck Index 9335
Kleeman & Engel p. 900
PDR p. 808
OCDS Vol. 1 p.241 (1977) & 2, 106 (1980)
I.N. p. 960
REM p. 851
Sonn, A.; U.S. Patent 2,161,938; June 13, 1939; assigned to the Society of Chemical Industry in Basle, Switzerland

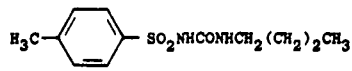
TOLBUTAMIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[(butylamino)carbonyl]-4-methylbenzenesulfonamide

Common Name: 1-butyl-3-(p-tolylsulfonyl)urea

Structural Formula:



Chemical Abstracts Registry No.: 64-77-7

Trade Name	Manufacturer	Country	Year Introduced
Dolipol	Hoechst	France	1956
Orinase	Upjohn	U.S.	1957
Abeformin T	Maruko	Japan	–
Aglicem	Wassermann	Spain	–
Aglycid	Wassermann	Italy	–
Artosin	Boehr. Mann.	W. Germany	–
Chembutamide	Chemo-Drug	Canada	–
Diabetol	Polfa	Poland	–
Diabeton	Teknofarma	Italy	–
Diabex-T	Funai	Japan	–
Diatol	Protea	Australia	–
Dirastan	Spofa	Czechoslovakia	–
Fordex	Martin Santos	Spain	–
Glyconon	D.D.S.A.	U.K.	–
Guabeta N	O.T.W.	West Germany	–
Insilange D	Horita	Japan	–
Mellitos D	Ono	Japan	–
Mobinol	Horner	Canada	–
Neo-Dibetic	Neo	Canada	–
Neo-Insoral	Valeas	Italy	–
Nigloid	Nippon Universal	Japan	–
Novobutamide	Novopharm	Canada	–
Oramide	I.C.N.	Canada	–
Oribetic	Cenci	U.S.	–
Orsinon	Teva	Israel	–
Oterben	Chinoin	Hungary	–
Pramidex	Berk	U.S.	–
Proinsul	Crosara	Italy	–
Rankmin	Maruishi	Japan	–
Rastinon	Hoechst	W. Germany	–
Takazide	Fuso	Japan	–
Tolbusal	Krka	Yugoslavia	–
Tolbutol	Smallwood	Canada	–
Tolubetin	Kwizda	Austria	–
Tolumid	A.F.I.	Norway	–
Toluvan	Zambeletti	Italy	–
Unimide	Sankyo	Japan	–
Urerubon	Seiko	Japan	–
Wescotol	Saunders	Canada	–

Raw Materials

n-Butyl isocyanate
Sodium 4-methylbenzenesulfonamide

Manufacturing Process

50 grams of n-butyl isocyanate are stirred at room temperature into a suspension of 96 grams of sodium 4-methyl-benzenesulfonamide in 120 cc of dry nitrobenzene and the whole is then heated for 7 hours at 100°C. After being cooled, the reaction mixture, which is a thick magma, is diluted with methylene chloride or ethyl acetate and the sodium salt of the sulfonylurea formed is separated by centrifuging. The centrifuged crystalline residue freed from organic solvents is dissolved in 500 to 600 cc of water heated at 50°C and decolorized with animal charcoal.

The precipitate obtained by acidification with dilute hydrochloric acid is dissolved in an equivalent quantity of dilute ammonia solution (about 1:20), again treated with animal charcoal and reprecipitated with dilute hydrochloric acid. In this manner N-4-methyl-benzenesulfonyl-N'-n-butyl-urea is obtained in analytically pure form in a yield of 70 to 80% of theory. It melts at 125° to 127°C (with decomposition).

References

Merck Index 9337
Kleeman & Engel p. 901
PDR pp. 830, 993, 1606, 1723, 1856, 1999
OCDS Vol. 1 p. 136 (1977) & 3, 62 (1984)
I.N. p. 961
REM p. 977
Ruschig, H., Aumüller, W., Korger, G., Wagner, H., Scholz, J. and Bänder, A.; U.S. Patent 2,968,158; January 17, 1961; assigned to The Upjohn Company

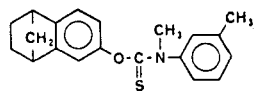
TOLCICLATE

Therapeutic Function: Topical antimycotic

Chemical Name: O-(1,4-Methano-1,2,3,4-tetrahydro-6-naphthyl)-N-methyl-N-(m-tolyl)-thiocarbamate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 50838-36-3

Trade Name	Manufacturer	Country	Year Introduced
Tolmicen	Carlo Erba	Italy	1979
Fungifos	Basotherm	W. Germany	1981
Kilmicen	Farmitalia	W. Germany	1983

Raw Materials

Thiophosgene
1,4-Methano-1,2,3,4-tetrahydro-6-naphthoxide
N-Methyl-m-toluidine

Manufacturing Process

Thiophosgene (1.15 g, 0.01 mol) in chloroform (40 ml) was slowly treated at room tempera-

ture with sodium 1,4-methano-1,2,3,4-tetrahydro-6-naphthoxide (1.82 g, 0.01 mol). After 30 minutes, N-methyl-m-toluidine (2.42 g, 0.02 mol) in chloroform (40 ml) was added dropwise to the solution so obtained at room temperature. The reaction mixture was stirred for 48 hours at room temperature and then refluxed for 2 hours. The solvent was evaporated, and the residue redissolved in water and extracted repeatedly with diethyl ether. The organic phase was dried (Na_2SO_4) and evaporated to dryness to give, after crystallization from isopropanol, O-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-N-methyl-N-(m-tolyl)-thiocarbamate (1.3 g) melting point 92°C to 94°C.

References

Merck Index 9338
DFU 1 (11) 543 (1976)
OCDS Vol. 3 p. 69 (1984)
DOT 17 (3) 94 (1981)
I.N. p. 961
Melloni, P., Metalli, R., Vecchietti, V., Logeman, W., De Carneri, I., Castellino, S. and Monti, G.; U.S. Patent 3,855,263; December 17, 1974; assigned to Carlo Erba SpA

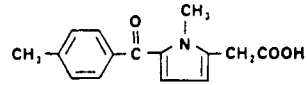
TOLMETIN

Therapeutic Function: Antiinflammatory

Chemical Name: 5-(p-Toluoyl)-1-methylpyrrole-2-acetic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 26171-23-3; 35711-34-3 (Na salt)

Trade Name	Manufacturer	Country	Year Introduced
Tolectin	McNeil	U.S.	1976
Tolectin	Cilag	Italy	1977
Tolectin	Cilag	W. Germany	1977
Tolectin	Ortho	U.K.	1979
Tolectin	Dainippon	Japan	1979
Reutol	Errekappa	Italy	–
Safitex	Montpellier	Argentina	–

Raw Materials

p-Toluoyl chloride
1-Methylpyrrole-2-acetonitrile
Sodium hydroxide

Manufacturing Process

5-(p-Toluoyl)-1-methylpyrrole-2-acetonitrile – To a cooled suspension of 26.6 g (0.2 mol) aluminum chloride in 80 ml dichloroethane is added dropwise 30.8 g (0.2 mol) p-toluoyl chloride. The resulting solution is added dropwise to a solution of 1-methylpyrrole-2-acetonitrile in 80 ml dichloroethane cooled externally with an ice bath. After the addition, the

resulting solution is stirred at room temperature for 20 minutes and then refluxed for 3 minutes. The solution is poured into ice acidified with dilute hydrochloric acid. The organic and aqueous fractions are separated. The aqueous fraction is extracted once with chloroform.

The organic fractions are combined and washed successively with N,N-dimethyl-1,3-propanediamine, dilute hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic fraction is dried over anhydrous magnesium sulfate. The solvent is then evaporated off. Upon trituration of the residue with methanol, a solid crystallizes, 5-(p-toluoyl)-1-methylpyrrole-2-acetonitrile, which is removed by filtration and purified by recrystallization from benzene.

Additional product is isolated from the mother liquors which are combined, concentrated in vacuo and the resulting oily residue column chromatographed on neutral alumina using hexane, benzene and ether as successive solvents. The product is isolated by concentrating in vacuo the first few major compound-bearing fractions (10% ether in benzene). The solids are combined and recrystallized from methanol and then from benzene-hexane, melting point 102°C to 105°C.

5-(p-Toluoyl)-1-methylpyrrole-2-acetic acid — A solution of 3.67 g (0.015 mol) of 5-(p-toluoyl)-1-methylpyrrole-2-acetonitrile, 24 ml of 1 N sodium hydroxide and 50 ml of 95% ethanol is stirred and refluxed for 24 hours.

The resulting solution is poured into ice acidified with dilute hydrochloric acid. A white solid precipitates which is extracted into ether. The ether phase is washed with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent is evaporated and a white solid, 5-(p-toluoyl)-1-methylpyrrole-2-acetic acid is obtained which is recrystallized twice from isopropanol, melting point 155°C to 157°C.

References

Merck Index 9346
Kleeman & Engel p. 902
PDR p. 1094
OCDS Vol. 2 p. 234 (1980)
DOT 8 (1) 39 (1972) & 11 (3) 109 (1975)
I.N. p. 962
REM p. 1121
Carson, J.R.; U.S. Patents 3,752,826; August 14, 1973; 3,865,840; February 11, 1975; and 3,952,012; April 20, 1976; all assigned to McNeil Laboratories, Inc.

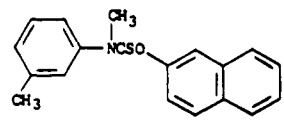
TOLNAFTATE

Therapeutic Function: Antifungal

Chemical Name: Methyl (3-methylphenyl)carbamothioic acid O-2-naphthalenyl ester

Common Name: Naphthiomate T

Structural Formula:



Chemical Abstracts Registry No.: 2398-96-1

Trade Name	Manufacturer	Country	Year Introduced
Tinactin	Schering	U.S.	1965
Tonoftal	Essex	W. Germany	1965
Tinaderm	Kirby-Warrick	U.K.	1967
Aftate	Plough	U.S.	–
Alarzin	Yamanouchi	Japan	–
Chinofungin	Chinoin	Hungary	–
Pitrex	Ikapharm	Israel	–
Separin	Sumitomo	Japan	–
Sorgoa	Scheurich	W. Germany	–
Sporiderm	Cetrane	France	–
Sporilene	Cetrane	France	–
Tinavet	Schering	W. Germany	–

Raw Materials

N-Methyl-3-toluidine
2-Naphthol
Thiophosgene

Manufacturing Process

In a first step, 2-naphthol is reacted with thiophosgene to give 2-naphthyl chlorothionoformate.

A mixture of 4.0 grams of N-methyl-3-toluidine and 2.8 grams of sodium hydrogencarbonate in 50 cc of acetone was stirred at 0° to 10°C and 7.4 grams of 2-naphthyl chlorothionoformate was added in small portions thereto and the mixture was heated under reflux for 30 minutes. The cooled mixture was poured into about 150 cc of cold water and 2-naphthyl-N-methyl-N-(3-tolyl)thionocarbamate was obtained as white crystals. Yield is 9.1 grams (90%). Recrystallization from alcohol gave colorless needle crystals, MP 110.5° to 111.5°C.

References

Merck Index 9347
Kleeman & Engel p. 903
PDR pp. 888, 1429
OCDS Vol. 2 p. 211 (1980) & 3, 69 (1984)
DOT 2 (1) 20 (1966)
I.N. p. 962
REM p. 1230
Miyazaki, K., Hashimoto, K., Kaji, A., Sakimoto, R., Taniguchi, K., Noguchi, T. and Igarashi, Y.; U.S. Patent 3,334,126; August 1, 1967; assigned to Nippon Soda KK, Japan

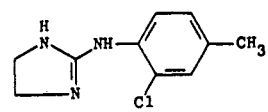
TOLONIDINE NITRATE

Therapeutic Function: Antihypertensive

Chemical Name: N-(2-Chloro-4-methylphenyl)-4,5-dihydro-1H-imidazol-2-amine

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 4201-23-4; 4201-22-3 (Base)

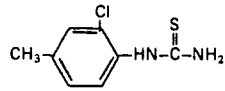
Trade Name	Manufacturer	Country	Year Introduced
Euctan	Essex	Switz.	1978
Euctan	Delalande	France	1978

Raw Materials

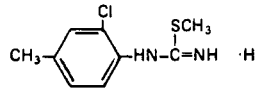
2-Chloro-4-methylaniline
Methyl iodide
Nitric acid
Ammonium thiocyanate
Ethylenediamine

Manufacturing Process

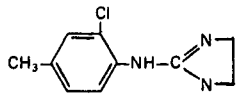
43 g of the thiourea compound (melting point 124°C) of the formula



obtained in known fashion from 2-chloro-4-methylaniline and ammonium thiocyanate and 20 cc of methyl iodide were dissolved in 200 cc of methanol, and the solution was refluxed for two hours. Thereafter, the solvent was evaporated in vacuo, leaving 73.2 g of the isothiouronium hydroiodide of the formula



as a residue. This isothiouronium salt was admixed with 20 cc of ethylenediamine, and the mixture was heated for about 30 minutes at 150°C to 160°C, accompanied by stirring; methyl mercaptan escaped during that time. Subsequently, the reaction mixture was taken up in hot dilute acetic acid, and the resulting solution was made alkaline with 2 N sodium hydroxide. A precipitate formed, which was separated by vacuum filtration, washed with water and dried. It was identified to be 2-(2'-chloro-4'-methylphenyl)-amino-1,3-diazacyclopentene-(2) of the formula



having a melting point of 142°C to 145°C. The yield was 10.2 g.

The nitrate of the base, obtained by acidifying a solution of the free base with nitric acid, had a melting point of 162°C to 164°C and was soluble in water and methanol.

References

Merck Index 9348
DFU 1 (5) 263 (1976)
Kleeman & Engel p. 903
DOT 15 (6) 303 (1979) & 18 (10) 550 (1982)
Zelle, K., Hauptmann, K.H. and Stahle, H.; U.S. Patent 3,236,857; February 22, 1966; and U.S. Patent 3,454,701; July 8, 1969; both assigned to Boehringer Ingelheim GmbH (Germany)

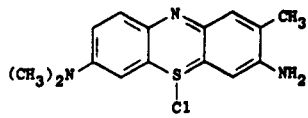
TOLONIUM CHLORIDE

Therapeutic Function: Coagulant

Chemical Name: 3-amino-7-(dimethylamino)-2-methylphenothiazin-5-ium chloride

Common Name: Dimethyltoluthionine chloride; blutene chloride; toluidine blue O

Structural Formula:



Chemical Abstracts Registry No.: 92-31-9

Trade Name	Manufacturer	Country	Year Introduced
Blutene	Abbott	U.S.	1953
Gabilin	Simons	W. Germany	–

Raw Materials

Dimethyl-p-phenylenediamine
Zinc
Sodium thiosulfate
Sodium nitrite
o-Toluidine
Zinc chloride

Manufacturing Process

As taken from U.S. Patent 416,055 (probably the oldest patent on the manufacture of a currently-used drug): In carrying out this process about 6 pbw of dimethyl-p-phenylenediamine was dissolved in about 18 pbw of hydrochloric acid of about 1.16 specific gravity and then a solution of about 3.8 pbw of nitrite of soda in about 6 pbw of water was gradually added. The hydrochlorate of nitroso-dimethylaniline thus produced in the well-known manner is then submitted to the reducing action of zinc-dust by adding, first about 30 pbw of hydrochloric acid of about 1.16 specific gravity and then (in small portions at a time) about 10 pbw of zinc-dust as is well understood by chemists. The solution of hydrochlorate of paramido-dimethylaniline thus obtained is afterwards diluted with about 250 pbw of water and then the uncombined hydrochloric acid contained in the solution is, if any, neutralized by the addition of an alkali. There are then added about 16 pbw of sulfate of alumina and about 13 pbw of thiosulfate of sodium, (hyposulfite of soda) and immediately afterwards a solution of about 5 pbw of bichromate of potash in about 60 pbw of water is quickly run in.

In this stage of the process the formation of an acid sulfureted compound of paramido-dimethylaniline takes place, possessing the formula $C_8H_{11}N_2S{\cdot}SO_3H$ (paramido-dimethyl-aniline-thiosulfonic acid). Without previous separation of this intermediate compound a solution of about 5.3 pbw of orthotoluidine, in the requisite amount of dilute hydrochloric acid (about 6 pbw of hydrochloric acid, SG about 1.16, diluted with about 6 pbw water) and shortly afterwards a solution of about 14 pbw of bichromate of potash in about 160 parts by weight of water is then added under constant agitation, when a precipitate will be formed chiefly consisting of a green indamine possessing in its dry condition the formula $C_{15}H_{17}N_3S_2O_3$. In order to transform the same into toluidine-blue, about 50 pbw of a solution of chloride of zinc of about 1.5 specific gravity are added and the mixture thus obtained is boiled during about half an hour, when, after cooling, the toluidine-blue thus formed will separate out and may then be filtered and purified, if necessary, by repeated solution in water and precipitation by means of chloride of sodium and chloride of zinc.

In the above described process the sulfate of alumina may be dispensed with and replaced

by as much hydrochloric, sulfuric, or acetic acid as will be required to liberate the thiosulfuric acid from the thiosulfate of sodium employed.

Toluidine-blue prepared as above described presents the following characteristic properties: It consists principally of the hydrochlorate of dimethyltoluthionine, the composition of which corresponds to the formula $C_{15}H_{15}N_3S \cdot HCl$.

References

Merck Index 9349
I.N. p. 962
Dändliker, G. and Bernthsen, H.A.; U.S. Patent 416,055; November 26, 1889; assigned to Badische Anilin and Soda Fabrik, Germany
March, B. and Moore, E.E.; U.S. Patent 2,571,593; October 16, 1951; assigned to Abbott Laboratories
Hoff, D.A.; U.S. Patent 2,809,913; October 15, 1957; assigned to The Warren-Teed Products Company

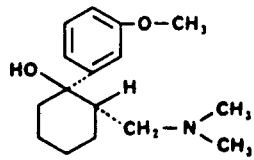
TRAMADOL HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: (±)-trans-2-[(Dimethylamino)methyl]-1-(m-methoxyphenyl)cyclohexanol hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 22204-88-2; 27203-92-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tramadol	Gruenenthal	W. Germany	1977
Crispin	Kowa	Japan	1978
Tramal	Gruenenthal	Switz.	1978

Raw Materials

m-Bromoanisole
2-Dimethylaminomethyl-cyclohexanone
Magnesium
Hydrogen chloride

Manufacturing Process

5 g of magnesium turnings are treated while stirring with a mixture of 37.4 g of m-bromoanisole and 160 ml of absolute tetrahydrofuran at such a rate that the reaction mixture boils gently because of the heat produced by the immediately starting reaction. Thereafter, the reaction mixture is boiled under reflux while stirring until all the magnesium dissolves. The reaction mixture is cooled to 0°C to -10°C and then a mixture of 23.25 g of 2-dimethylaminomethyl-cyclohexanone and 45 ml of absolute tetrahydrofuran is added dropwise.

The resulting mixture is stirred for 4 hours at room temperature and then poured, while stir-

ring slowly, into a mixture of 25 g of ammonium chloride, 50 ml of water and 50 g of ice. The layers are separated and the aqueous layer is extracted twice with 50 ml portions of ether. The organic layers are combined, dried with sodium sulfate and evaporated. The residue is distilled, and 1-(m-methoxyphenyl)-2-dimethylaminomethyl-cyclohexanol-(1), boiling point at 0.6 mm Hg 138°C to 140°C, is obtained in a yield of 78.6% of theoretical.

The hydrochloride obtained from the product, e.g., by dissolving in ether and treating with dry hydrogen chloride, melts at 168°C to 175°C. By recrystallization from moist dioxan this hydrochloride is separated into isomers melting at 162°C to 163°C and 175°C to 177°C, respectively.

References

Merck Index 9388
Kleeman & Engel p. 906
OCDS Vol. 2 p. 17 (1980)
DOT 13 (8) 345 (1977)
I.N. p. 966
Chemie Grunenthal GmbH; British Patent 997,399; July 7, 1965
Flick, K. and Frankus, E.; U.S. Patent 3,652,589; March 28, 1972; assigned to Chemie Grunenthal GmbH

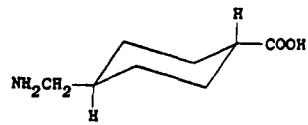
TRANEXAMIC ACID

Therapeutic Function: Coagulant

Chemical Name: trans-4-(aminomethyl)cyclohexanecarboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1197-18-8

Trade Name	Manufacturer	Country	Year Introduced
Anvitoff	Knoll	W. Germany	1967
Transamin	Bayer-Daiichi	Japan	1970
Ugorol	Bayer	Italy	1970
Frenolyse	Specia	France	1971
Cyklokapron	Kabi	U.K.	1978
Amcacid	Bonomelli-Hommel	Italy	–
Amchafibrin	Fides	Spain	–
Amikapron	Kabi-Vitrum	Sweden	–
Carxamin	Sankyo	Japan	–
Emorhalt	Bayropharm	W. Germany	–
Exacyl	Choay	France	–
Hexakapron	Teva	Israel	–
Hexapromin	Kowa	Japan	–
Hexatron	Nippon Shinyaku	Japan	–
Mastop	Sawai	Japan	–
Rikaverin	Toyo Jozo	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Spiramin	Mitsui	Japan	–
Tranex	Malesci	Italy	–
Tranexan	Taiyo	Japan	–
Transamin	Daiichi	Japan	–
Transamlon	Toho	Japan	–
Vasolamin	Daiichi	Japan	–

Raw Materials

p-Aminomethylbenzoic acid
Hydrogen

Manufacturing Process

In an autoclave, 2 grams of a mixture of cis- and trans-4-aminomethylcyclohexane-1-carboxylic acid, which is obtained by catalytic reduction of p-aminomethylbenzoic acid in the presence of platinum catalyst and contains 60% by weight of cis-isomer was reacted at 200°C, for 8 hours with 20 ml of ethyl alcohol in which 0.44 gram of sodium metal had been dissolved. After cooling, the reaction solution was concentrated under a reduced pressure to give a white residue. This residue was dissolved in 40 ml of water and passed through a column of a strongly acidic cation ion-exchanger resin (NH_4^+). The eluate was concentrated under reduced pressure to form a white mass. An adequate amount of acetone was added thereto and 1.95 grams of white powder was obtained. This powder was recrystallized from water-acetone to give 1.85 grams (yield, 92.5%) of white crystalline powder having a melting point of 380° to 390°C (decomposition). This product was identified as trans-4-aminomethylcyclohexane-1-carboxylic acid by means of infrared spectrum.

References

Merck Index 9390
Kleeman & Engel p. 907
OCDS Vol. 2 p. 9 (1980)
DOT 2 (1) 26 (1966)
I.N. p. 39
REM p. 831
Naito, T., Okano, A., Aoyagi, T., Miki, T., Kadoya, S., Inaoka, M. and Shindo, M.; U.S. Patent 3,499,925; March 10, 1970; assigned to Daiichi Seiyaku Company Limited, Japan and Mitsubishi Chemical Industries Limited, Japan

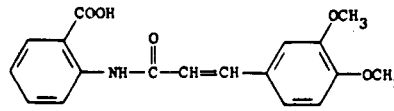
TRANILAST

Therapeutic Function: Antiallergic

Chemical Name: 2-[[3-(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl] amino] -benzoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53902-12-8

Trade Name	Manufacturer	Country	Year Introduced
Rizaben	Kissei	Japan	1982

Raw Materials

3,4-Dimethoxycinnamic acid
Methyl anthranilate
Benzene sulfonyl chloride
Sodium hydroxide

Manufacturing Process

4 g of 3,4-dimethoxycinnamic acid was dissolved in 20 ml of dry pyridine. To this solution were added under cooling with ice and agitation 2 g of benzenesulfonyl chloride whereby a red orange precipitate was formed. The reaction mixture was stirred for about one hour and then 2 g of methyl anthranilate were added to the mixture under cooling with ice. The mixture was stirred for 2 hours at room temperature to complete the reaction. After completion of the reaction, the reaction mixture was concentrated and the residue was taken up in about 10 ml of chloroform. The solution was washed first with a 10% aqueous solution of caustic soda, then with a 10% aqueous solution of hydrochloric acid and finally with water and then distilled to remove chloroform whereby crystals of N-(3',4'-dimethoxycinnamoyl)-anthranilic acid methyl ester were obtained.

This product was dissolved in 10 ml of chloroform. To this solution were added 10 ml of a 10% aqueous solution of caustic soda and the mixture was warmed at 50°C to effect hydrolysis of the ester group. After completion of the reaction, the organic phase was separated, washed with water and distilled to remove the solvent whereby 2.1 g (yield: 48%) of the end product, i.e., N-(3',4'-dimethoxycinnamoyl)-anthranilic acid, were obtained. This product had a melting point of 211°C to 213°C.

References

Merck Index 9392
DFU 7 (12) 907 (1982)
DOT 19 (2) 114 & (9) 485 (1983)
I.N. p. 966
Harita, K., Ajisawa, Y., Iizuka, K., Kinoshita, Y., Kamijo, T. and Kobayashi, M.; U.S. Patent 3,940,422; February 24, 1976; assigned to Kissei Yakuhin Kogyo K.K. (Japan)

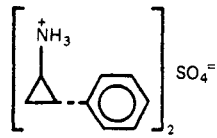
TRANYLCYPROMINE SULFATE

Therapeutic Function: Psychostimulant

Chemical Name: trans(±)-2-phenylcyclopropanamine sulfate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 13492-01-8; 155-09-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Parnate	SKF	U.K.	1960
Parnate	SKF	U.S.	1961

Trade Name	Manufacturer	Country	Year Introduced
Tylciprine	Theraplix	France	1963
Parnate	Rohm	W. Germany	1969
Parmodalin	Maggioni	Italy	—

Raw Materials

Styrene
Sodium hydroxide
Sodium azide
Sulfuric acid
Ethyl diazoacetate
Thionyl chloride
Hydrogen chloride

Manufacturing Process

A solution containing 167 grams of stabilized styrene and 183 grams of ethyl diazoacetate is cooled to 0°C and dropped into 83.5 grams of styrene with stirring, in a dry nitrogen atmosphere, at 125° to 135°C. This produced the ester ethyl 2-phenylcyclopropanecarboxylate.

A solution of the above ester (207.8 grams) and 64.5 grams of sodium hydroxide in 80 cc of water and 600 cc of ethanol is refluxed for 9 hours. The carboxylic acid of 2-phenylcyclopropane is liberated with 200 cc of concentrated hydrochloric acid. The 2-phenylcyclopropanecarboxylic acid contains 3 to 4 parts of the trans isomer to 1 part of the cis isomer. The acid is recrystallized from hot water. The pure trans isomer comes out as crystalline material (solid) while the cis isomer stays in solution.

A solution of 4.62 grams of 2-phenylcyclopropanecarboxylic acid in 15 cc of dry benzene is refluxed with 4 cc of thionyl chloride for 5 hours, the volatile liquids are removed and the residue once more distilled with benzene. Fractionation of the residue yields the carbonyl chloride of 2-phenylcyclopropane.

A mixture of 15 grams of technical sodium azide and 50 cc of dry toluene is stirred and warmed and a solution of 10 grams of 2-phenylcyclopropanecarbonyl chloride in 50 cc of dry toluene is added slowly. Inorganic salts are filtered and washed well with dry benzene and the solvents are removed under reduced pressure. The $RCON_3$ compound produced undergoes the Curtius rearrangement to $RNCO + N_2$. The residual isocyanate is a clear red oil of characteristic odor. It is cooled to 10°C and treated cautiously with 100 cc of 35% hydrochloric acid whereupon $RNCO + H_2O$ gives $RNH_2 + CO_2$. After most of the evolution of carbon dioxide has subsided the mixture is refluxed for 13 hours, the cooled solution is diluted with 75 cc of water and extracted with three 50 cc portions of ether. The acid solution is evaporated under reduced pressure with occasional additions of toluene to reduce foaming.

The almost dry residue is cooled to 0°C and made strongly alkaline with a 50% potassium hydroxide solution. The amine is extracted into several portions of ether, dried over potassium hydroxide, the solvent removed, and the base fractioned. Reaction of the base with a half-molar quantity of sulfuric acid gives the sulfate.

References

Kleeman & Engel p. 907
PDR p. 1719
OCDS Vol. 1 p. 73 (1977) & 2, 7, 50 (1980)
I.N. p. 967
REM p. 1097
Tedeschi, R.E.; U.S. Patent 2,997,422; August 22, 1961; assigned to Smith Kline & French Laboratories

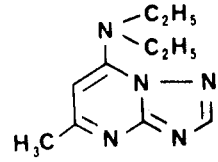
TRAPIDIL

Therapeutic Function: Coronary vasodilator

Chemical Name: 5-Methyl-7-diethylamino-1-triazolo-(1,5-a)-pyrimidine

Common Name: Trapymin

Structural Formula:



Chemical Abstracts Registry No.: 15421-84-8

Trade Name	Manufacturer	Country	Year Introduced
Rocornal	Mochida	Japan	1978
Rocornal	Deutsches Hydrierwerk	E. Germany	—

Raw Materials

5-Methyl-7-chloro-s-triazolo-(1,5-a)-pyrimidine
Diethylamine

Manufacturing Process

8.4 g of 5-methyl-7-chloro-s-triazolo-(1,5-a)-pyrimidine were suspended in 30 cc of water and 7.3 g of diethylamine added. After 2 hours heating with stirring, the mixture was concentrated under vacuum. The residue was recrystallized from n-heptane. This process yielded 8.1 g of the 5-methyl-7-diethylamino-s-triazolo-(1,5-a)-pyrimidine having a melting point of 103°C to 104°C. The hydrochloride produced in the usual manner had a melting point of 212°C.

References

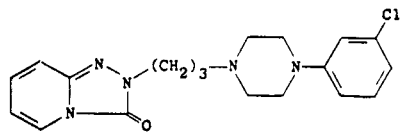
Merck Index 9396
DOT 8 (1) 25 (1972)
I.N. p. 967
Tenor, E., Fuller, H. and Hausschild, F.; British Patent 1,148,629; April 16, 1969; assigned to Veb. Deutsches Hydrierwerk Rodleben

TRAZODONE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl] -1,2,4-triazolo[4,3-a] -pyridin-3(2H)-one hydrochloride

Structural Formula:



(base)

Chemical Abstracts Registry No.: 25332-39-2; 19794-93-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Trittico	Angelini	Italy	1972
Thombran	Thomae	W. Germany	1977
Pragmazone	U.P.S.A.	France	1980
Molipaxin	Roussel	U.K.	1980
Desyrel	Bristol	Canada	1982
Desyrel	Mead Johnson	U.S.	1982
Beneficat	Nemi	Argentina	—
Bimaran	Roux-Ocefa	Argentina	—
Manegan	Argentia	Argentina	—
Tramensan	Medica	Finland	—

Raw Materials

2-Chloropyridine
Semicarbazide
Sodium hydride
1-(3-Chloropropyl)-4-m-chlorophenylpiperazine

Manufacturing Process

In an initial step, 2-chloropyridine is reacted with semicarbazide to give s-triazolo-[4,3-a]-pyridine-3-one.

To a boiling solution of 6.7 grams s-triazolo-[4,3-a]-pyridine-3-one in 80 ml dioxane, there is added 2.4 grams 50% NaH. The mixture is refluxed during 1 hour under stirring, then 13.5 grams 1-(3-chloropropyl)-4-m-chlorophenylpiperazine is added. The mixture is refluxed under stirring for 20 hours, cooled, diluted with an equal volume of ether, the sodium chloride filtered out, and ethereal HCl added. The solid which precipitates is filtered out and crystallized from 95% alcohol. Yield is 13.5 grams, MP 223°C.

The following is an alternative method of preparation: 1 gram 2-(γ-chloropropyl)-s-triazolo-[4,3-a]-pyridine-3-one and 5 ml saturated ammonia alcoholic solution are heated for 5 hours in a closed tube at 100°C. The contents of the tube are cooled, the ammonium chloride filtered out and the solvent is removed. There remains a residue of 0.9 grams 2-(γ-aminopropyl)-s-triazolo-[4,3-a]-pyridine-3-one.

This residue is dissolved in isopropyl alcohol and 1 gram N-bis-chloroethyl-aniline is added to it. The mixture is refluxed for 3 hours. The solvent is removed at a reduced pressure, the residue is treated with 50% potassium carbonate, and extracted with ether. By treating with ethereal hydrochloric acid, 2-N'-m-chlorophenylpiperazino-propyl-s-triazole-[4,3-a]-pyridine-3-one hydrochloride is precipitated; MP 223°C.

References

Merck Index 9398
Kleeman & Engel p. 908
PDR p. 1123
OCDS Vol. 2 p. 472 (1980)
DOT 9 (3) 115 (1973)
I.N. p. 968
REM p. 1097
Palazzo, G. and Silvestrini, B.; U.S. Patent 3,381,009; April 30, 1968; assigned to Aziende Chimiche Riunite Angelini Francesco a Roma, Italy