T

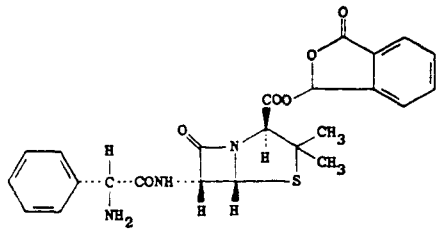
TALAMPICILLIN

Therapeutic Function: Antibacterial

Chemical Name: (2S)-6-[(aminophenylacetyl)amino] -3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0] heptane-2-carboxylic acid 1,3-dihydro-3-oxo-1-isobenzofuranyl ester

Common Name: Phthalidyl-D-α-aminobenzylpenicillanate

Structural Formula:



Chemical Abstracts Registry No.: 47747-56-8; 39878-70-1 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Talpen	Beecham	U.S.	1975
Yamacillin	Yamanouchi	Japan	1977
Talampicillina	Midy	Italy	1980
Talat	Polifarma	Italy	–
Talmen	Prodes	Spain	–

Raw Materials

Ampicillin
3-Bromophthalide

Manufacturing Process

A fine suspension of 25.18 grams (0.05 mol) of potassium salt of enamine protected ampicillin and 10.65 grams (0.05 mol) 3-bromophthalide were reacted in a 1:2 mixture of acetone/ethyl acetate (1,500 ml) for 24 hours. After filtration the organic layer was washed twice with 250 ml portions of 1 N sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. Addition of ether crystallized the phthalide enamine protected α-aminophenylacetamido penicillanate in 85% yield.

The enamine protecting group was removed by dissolving 10 grams in aqueous acetone (250 ml water to 250 ml acetone) and vigorously stirring this solution at pH 2.5 for 1 hour. The acetone was removed in vacuo and the ester, which was salted out of the aqueous phase as a sticky yellow gum, was dissolved in ethyl acetate (200 ml) and washed twice with 200 ml portions of 1 N sodium bicarbonate and brine and dried over anhydrous magnesium sulfate. Careful addition of dry ester (about 50 ml) to the dry ethyl acetate layer

yielded the ampicillin phthalide ester as hydrochloric salt as a fine white amorphous solid in 80% yield.

References

Merck Index 8912
Kleeman & Engel p. 854
OCDS Vol. 2 p. 438 (1980)
DOT 12 (7) 283 (1976) & 15 (8) 349 (1979)
I.N. p. 919
REM p. 1201
Ferres, H.; U.S. Patent 3,860,579; January 14, 1975; assigned to Beecham Group Limited, England
Murakami, M., Isaka, I., Kashiwagi, T., Matsui, H., Nakano, K., Takahashi, K., Horiguchi, H. and Koda, A.; U.S. Patent 3,951,954; April 20, 1976; assigned to Yamanouchi Pharmaceutical Co., Ltd., Japan

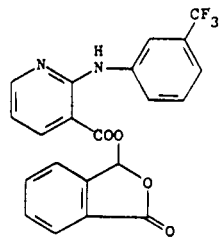
TALNIFLUMATE

Therapeutic Function: Antiinflammatory, analgesic

Chemical Name: 2-[[3-(Trifluoromethyl)phenyl] amino] -3-pyridine carboxylic acid 1,3-dihydro-3-oxo-1-isobenzofuranyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 66898-62-2

Trade Name	Manufacturer	Country	Year Introduced
Somalgen	Bago	Argentina	1972

Raw Materials

2-(3'-Trifluoromethylanilino)nicotinic acid
3-Bromophthalide

Manufacturing Process

49 ml of triethylamine were added to a suspension of 2-(3'-trifluoromethylanilino)nicotinic acid (70.6 g in 250 ml of dimethylformamide). After stirring for 30 minutes 53.3 g of 3-bromophthalide were added. The reaction mixture was maintained at 25°C to 30°C during 4 hours. Ethyl acetate (750 ml) was poured into the reaction mixture. This solution was filtered and extracted with water (4 X 250 ml), discarding the water layer.

The organic layer was dried with anhydrous magnesium sulfate and then filtered. The solution was concentrated under vacuum at 30°C to 35°C until reduced to half of its original volume and then cooled to 5°C to allow the crystallization of the compound. Thus, the cake was filtered, washed with cool ethyl acetate, and dried under vacuum. Yield: 74% (76.7 g) of phthalidyl ester of 2-(3'-trifluoromethylanilino)-pyridin-3-carboxylic acid, melting point: 165°C to 167°C.

References

Merck Index 8921
DFU 4 (6) 448 (1979)
OCDS Vol. 3 p. 146 (1984)
DOT 19 (7) 99 (1983)
I.N. p. 919
Bago, S.; U.S. Patent 4,168,313; September 18, 1979

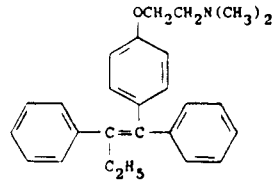
TAMOXIFEN

Therapeutic Function: Antiestrogen, antineoplastic

Chemical Name: 2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 10540-29-1; 54965-24-1 (Citrate)

Trade Name	Manufacturer	Country	Year Introduced
Nolvadex	I.C.I.	U.K.	1973
Nolvadex	I.C.I.	W. Germany	1976
Nolvadex	I.C. Pharma	Italy	1976
Nolvadex	I.C.I.	France	1977
Nolvadex	I.C.I.	Switz.	1978
Nolvadex	Stuart	U.S.	1978
Nolvadex	Sumitomo	Japan	1981
Tamofen	Rhone-Poulenc	–	–
Valodex	Abic	Israel	–

Raw Materials

Bromobenzene
Magnesium
4-(β-Dimethylaminoethoxy)-α-ethyldesoxybenzoin

Manufacturing Process

To the Grignard reagent prepared from 0.59 part of magnesium, 3.95 parts of bromobenzene

and 50 parts of ether there are added 7.5 parts of 4-(β-dimethylaminoethoxy)-α-ethyldesoxybenzoin in 50 parts of ether. After heating under reflux for 3 hours, the mixture is decomposed by the addition of a solution of 60 parts of ammonium chloride in 150 parts of water. The mixture is separated, and the ethereal layer is dried with anhydrous sodium sulfate, and the ether is evaporated. The residue is crystallized from methanol. There is thus obtained 1-(p-β-dimethylaminoethoxyphenyl)-1,2-diphenylbutan-1-ol, melting point 120°C to 121°C.

2.15 parts of 1-(p-β-dimethylaminoethoxyphenyl)-1,2-diphenylbutan-1-ol, 25 parts of ethanol and 0.8 part of 10N hydrochloric acid are heated together under reflux for 3 hours. The solution is evaporated to dryness under reduced pressure and the residue is extracted with methylene chloride. The methylene chloride extract is decolorized with charcoal and then evaporated to dryness. The residue is dissolved in 100 parts of water, the solution is basified by the addition of sodium hydroxide solution, and the precipitated solid is extracted three times, each time with 50 parts of ether. The combined extracts are dried with anhydrous sodium sulfate and then evaporated. The residue is crystallized from aqueous methanol, and there is thus obtained 1-(p-β-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene, melting point 95°C to 96°C.

References

Merck Index 8923
Kleeman & Engel p. 854
PDR p. 1783
OCDS Vol. 2 p. 127 (1980) & 3, 70 (1984)
DOT 10 (2) 71 (1974)
I.N. p. 920
REM p. 990
Harper, M.J.K., Richardson, D.N. and Walpole, A.L.; British Patent 1,013,907; December 22, 1965; assigned to Imperial Chemical Industries, Ltd. (U.K.)

TANPHETAMIN

Therapeutic Function: Antiobesity drug

Chemical Name: d-Amphetamine tannate

Common Name: Dexamphetamine tannate

Structural Formula: A complex of amphetamine, $C_6H_5CH_2CH(CH_3)NH_2$ and tannic acid

Chemical Abstracts Registry No.: 1407-85-8

Trade Name	Manufacturer	Country	Year Introduced
Synatan	Neisler	U.S.	1955
Obotan	Mallinckrodt	U.S.	—
Proptan	Irwin, Neisler	U.S.	—

Raw Materials

d-Amphetamine
Tannic acid

Manufacturing Process

Approximately 75 grams of d-amphetamine as a free base was dissolved in 300 ml of isopropanol (solution A). Approximately 200 grams of NF tannic acid was dissolved in 700

milliliters of slightly warmed isopropanol (solution B). Solution B was poured, with rapid stirring, into solution A to provide an almost immediate precipitation of the insoluble tannate complex. The solution was cooled to room temperature and the product filtered off and dried. During the filtration, most of the isopropanol was removed by washing with acetone, and the precipitate dried at 140°F to yield a light tan product. The amount of precipitate was approximately 200 grams of tannate salt but more could be obtained by concentration of the mother liquors.

References

Merck Index 8930
I.N. p. 301
Cavallito, C.J.; U.S. Patent 2,950,309; August 23, 1960; assigned to Irwin, Neisler and Company

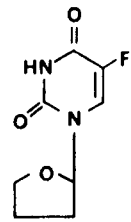
TEGAFUR

Therapeutic Function: Antineoplastic

Chemical Name: 1-(Tetrahydro-2-furanyl)-5-fluorouracil

Common Name: Ftorafur

Structural Formula:



Chemical Abstracts Registry No.: 17902-23-7

Trade Name	Manufacturer	Country	Year Introduced
Futraful	Taiho	Japan	1974
Ftorafur	Gruenenthal	W. Germany	1977
Citofur	Lusofarmaco	Italy	1981
Futraful	Simes	Italy	1981
Coparogin	Nippon Chemiphar	Japan	–
Daiyalose	Daito	Japan	–
Exonal	Toyama	Japan	–
Fental	Kanebo	Japan	–
F.H.	Mitsui	Japan	–
Filacul	Torii	Japan	–
Flopholin	Tsuruhara	Japan	–
Franroze	Hishiyama	Japan	–
Ftoral	Abic	Israel	–
F.T.R.	Tenyosha	Japan	–
Fulaid	Takeda	Japan	–
Fulfeel	Kyorin	Japan	–
Furofluor	Green Cross	Japan	–
Furofutran	Taiyo	Japan	–
Futraful Zupo	Taiho	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Geen	Tatumi	Japan	–
Helpa	Teikoru	Japan	–
Icalus	Isei	Japan	–
Lamar	Tokyo Tanabe	Japan	–
Lifril	Kissei	Japan	–
Lunacin	Sawai	Japan	–
Natira	Mohan	Japan	–
Neberk	Fuji	Japan	–
Nitobanil	Ohta	Japan	–
Pharmic	Toyo	Japan	–
Rescrel	Nikken	Japan	–
Richina	Taiyo	Japan	–
Riol	Toa Eiyo	Japan	–
Sinoflurol	Kaken	Japan	–
Sunfural	Toyo Jozo	Japan	–
Tefsiel	Towa	Japan	–
THF-FU	Taiho	Japan	–
Utefos	Almirall	Spain	–
Videcocan	Unifa	Argentina	–
Youfural	Showa	Japan	–

Raw Materials

2,4-Bis(trimethylsilyl)-5-fluorouracil
Ammonia
2-Chlorofuranidin
2,3-Dihydrofuran
5-Fluorouracilmercury

Manufacturing Process

One process from U.S. Patent 4,107,162: 27.4 g of 2,4-bis(trimethylsilyl)-5-fluorouracil and 7.7 g of 2,3-dihydrofuran are dissolved in 70 ml of acetonitrile, and 30 ml of an acetonitrile solution containing 1.3 g of anhydrous stannic chloride are added thereinto with cooling and stirring. 50 ml of acetonitrile containing 1.3 ml of water dissolved therein are then dropwise added over 15 minutes. After return to room temperature, the reaction is further effected with stirring at 40°C for 5 hours. The reaction mixture is neutralized by adding 1 N aqueous ammonia with cooling and stirring (conversion 83%). After the nondissolved substances are removed by filtration, the filtrate is concentrated and dried under reduced pressure. 100 ml of water and 300 ml of dichloromethane are added to the residue to completely dissolve the residue by stirring. The obtained dichloromethane layer is separated. The water layer is subjected to extraction twice with dichloromethane. The thus obtained extracts are combined with the separated dichloromethane layer and the combined extracts, after drying with anhydrous magnesium sulfate, are concentrated and dried. The obtained residue is dissolved in ethanol, and the nondissolved substances are removed by filtration. The filtrate is subjected to recrystallization to give white crystals, followed by further recrystallization of the mother liquor. There are totally obtained 15.6 g of N_1-(2'-furanidyl)-5-fluorouracil. Yield: 78% of theory, with respect to 2,4-bis(trimethylsilyl)-5-fluorouracil.

An alternative process from U.S. Patent 3,635,946: A vigorously stirred reaction mixture consisting of 32.87 g (0.1 mol) of 5-fluorouracilmercury, 100 ml of dimethylformamide and 50 ml of toluene is dried by azeotropic distillation of toluene. It is then cooled to -40°C in a stream of dry nitrogen, and a solution of 21.3 g (0.2 mol) of 2-chlorofuranidin in 20 ml of dried dimethylformamide is gradually added to the stirred mixture, the temperature being maintained between -40°C and -30°C. After completion of the reaction (which is marked by complete dissolution of the starting 5-fluorouracilmercury) i.e. after about 3 to 4 hours, 60 to 80 ml of the solvent are distilled off in vacuo at a bath temperature not exceeding 35°C; 50 to 70 ml of dry acetone are then added and also vacuum distilled. The residue is easily crystallized. It is collected, washed three times with small quantities of ethanol–10 ml each–and air-dried. 12.2 g of N_1-(2'-furanidyl)-5-fluorouracil are obtained in the form of white crystal-

line solids; melting point 160°C to 162°C. Additional treatment of the mother liquor yields 3.0 g more of the product. Yield: 75% of theory, based on the starting 5-fluorouracilmercury.

After recrystallization from ethanol, 14.3 g of N_1-(2'-furanidyl)-5-fluorouracil are obtained, MP 164°C to 165°C.

References

Merck Index 8963
Kleeman & Engel p. 855
OCDS Vol. 3 p. 155 (1984)
I.N. p. 923
Townsend, L.B., Earl, R.A. and Manning, S.J.; U.S. Patent 3,960,864; June 1, 1976; assigned to The University of Utah
Giller, S.A., Zhuk, R.A., Lidak, M.J. and Zidermane, A.A.; U.S. Patent 3,635,946; Jan. 18, 1972
Suzuki, N., Kobayashi, Y., Hiyoshi, Y., Takagi, S., Sone, T., Wakabayashi, M. and Sowa, T.; U.S. Patent 4,107,162; August 15, 1978; assigned to Asahi Kasei Kogyo K.K. (Japan)

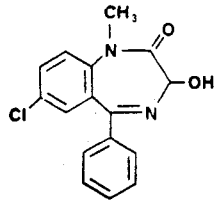
TEMAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 846-50-4

Trade Name	Manufacturer	Country	Year Introduced
Levanxol	Carlo Erba	Italy	1970
Euhypnos	Montedison	U.K.	1977
Normison	Wyeth	U.K.	1977
Restoril	Sandoz	U.S.	1981
Planum	Carlo Erba	W. Germany	1981
Normison	Wyeth Byla	France	1981
Euhypnos	Farmitalia	France	1981
Normison	Wyeth	Switz.	1983
Planum	Carlo Erba	Switz.	1983
Mabertin	Sidus	Argentina	–
Maeva	Ravizza	Italy	–
Signopam	Polfa	Poland	–

Raw Materials

3-Acetoxy-7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one
Sodium hydroxide

Manufacturing Process

According to British Patent 1,022,645 3.4 g of 3-acetoxy-7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one suspended in 80 ml alcohol was treated with 6 ml of 4 N NaOH. After complete solution had taken place, a solid precipitated; this solid was redissolved by the addition of 80 ml of water. The solution was acidified with acetic acid to give white crystals which were recrystallized from alcohol to yield 7-chloro-3-hydroxy-5-phenyl-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, MP 119° to 121°C.

References

Merck Index 8976
Kleeman & Engel p. 856
PDR p. 1591
OCDS Vol. 2 p. 402 (1980)
DOT 6 (6) 224 (1970) & 9 (6) 238 (1973)
I.N. p. 923
REM p. 1064
American Home Products Corporation; British Patent 1,022,642; March 16, 1966
American Home Products Corporation; British Patent 1,022,645; March 16, 1966
Bell, S.C.; British Patent 1,057,492; February 1, 1967; assigned to American Home Products Corporation

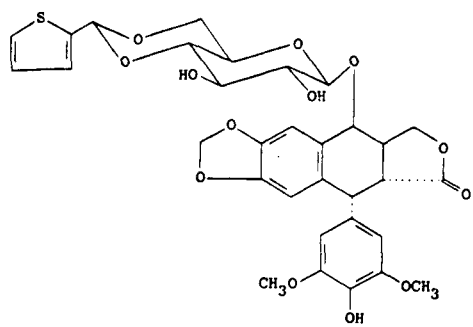
TENIPOSIDE

Therapeutic Function: Antineoplastic

Chemical Name: 4'-Demethylepipodophyllotoxin-β-D-thenylidene glucoside

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 29767-20-2

Trade Name	Manufacturer	Country	Year Introduced
Vehem	Sandoz	France	1976
Vumon	Bristol	W. Germany	1980
Vumon	Bristol	Switz.	1980
Vumon	Bristol	Italy	1982

Raw Materials

4'-Demethylepipodophyllotoxin-β-D-glucoside
Thiophene-2-aldehyde

Manufacturing Process

10 ml of pure thiophene-2-aldehyde and 0.25 g of anhydrous zinc chloride are added to 0.5 g of dried 4'-demethylepipodophyllotoxin-β-D-glucoside and the mixture is shaken on a machine at 20°C in the absence of moisture, whereupon a clear solution is gradually obtained. The course of condensation is checked by thin layer chromatography. After a reaction period of 3 to 4 hours the solution is diluted with chloroform and shaken out with water. The chloroform phase is washed twice more with a small amount of water and then dried over sodium sulfate and concentrated by evaporation. Excess thiophene-2-aldehyde is removed by dissolving the resulting residue in a small amount of acetone and reprecipitation is effected by adding pentane.

Reprecipitation from acetone/pentane is repeatedly effected until the condensation product sults in flaky form. Further purification is effected in that the crude product is chromatographed on silica gel. The fractions which are uniform in accordance with thin layer chromatography are combined and yield crystals from absolute alcohol. Pure 4'-demethylepipodophyllotoxin-β-D-thenylidene glucoside has a melting point of 242°C to 246°C (last residue up to 255°C).

References

Merck Index 8978
Kleeman & Engel p. 857
DOT 12 (11) 465 (1976) & 16 (5) 170 (1980)
I.N. p. 924
REM p. 1156
Keller-Juslen, C., Kuhn, M., Renz, J. and von Wartburg, A.; U.S. Patent 3,524,844; Aug. 18, 1970; assigned to Sandoz, Ltd. (Switz.)

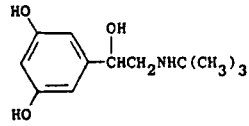
TERBUTALINE

Therapeutic Function: Bronchodilator

Chemical Name: 1-(3',5'-Dihydroxyphenyl)-2-(t-butylamino)-ethanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 23031-25-6; 23031-32-5 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Bricanyl	Pharma-Stern	W. Germany	1971
Bricanyl	Astra	U.K.	1971
Bricanyl	Lematte-Boinot	France	1973
Bricanyl	Astra	U.S.	1974

Trade Name	Manufacturer	Country	Year Introduced
Bricanyl	Fujisawa	Japan	1974
Brethine	Ciba Geigy	U.S.	1975
Terbasmin	Farmitalia	Italy	1976
Arubendol	Ankerwerk	E. Germany	–
Brethaire	Ciba Geigy	U.S.	–
Bricalin	Teva	Israel	–
Brican	Draco	Sweden	–
Bristurin	Bristol	Japan	–
Filair	Riker	U.K.	–

Raw Materials

Benzyl-t-butylamine
3,5-Dibenzyloxy-ω-bromoacetophenone
Hydrogen

Manufacturing Process

To a solution of 32 g of benzyl-t-butylamine in 300 ml of absolute ethanol at reflux temperature was added 32 g of 3,5-dibenzyloxy-ωbromoacetophenone in 10 ml of dry benzene. The mixture was refluxed for 20 hours and then evaporated. When absolute ether was added to the residue, benzyl-t-butylamine hydrobromide was precipitated. The precipitated compound was filtered off and to the filtrate was added an excess of 2N sulfuric acid. This caused precipitation of the hydrogen sulfate of 3,5-dibenzyloxy-ω-(benzyl-t-butylamino)-acetophenone which was recrystallized from acetone/ether. If the product is crystallized from different organic solvents, the melting point will vary with the type and amount of solvent of crystallization, but the product can be used directly for hydrogenation.

15 g of 3,5-dibenzyloxy-ω-(benzyl-t-butylamino)-acetophenone hydrogen sulfate in 200 ml of glacial acetic acid were hydrogenated in a Parr pressure reaction apparatus in the presence of 1.5 g of 10% palladium charcoal at 50°C and 5 atmospheres pressure. The reaction time was 5 hours. The catalyst was filtered off, the filtrate was evaporated to dryness and the hydrogen sulfate of 1-(3',5'-dihydroxyphenyl)-2-(t-butylamino)-ethanol was received. This compound is hygroscopic, but it can be transformed into a nonhygroscopic sulfate in the following manner.

The hydrogen sulfate was dissolved in water and the pH of the solution was adjusted to 5.6 (pH-meter) with 0.1 N sodium hydroxide solution. The water solution was evaporated to dryness and the residue dried with absolute ethanol/benzene and once more evaporated to dryness. The remaining crystal mixture was extracted in a Soxhlet extraction apparatus with absolute methanol. From the methanol phase the sulfate of 1-(3',5'-dihydroxyphenyl)-2-(t-butylamino)-ethanol crystallized. Melting point 246°C to 248°C.

References

Merck Index 8986
Kleeman & Engel p. 858
PDR pp. 889, 987
I.N. p. 925
REM p. 890
Wetterlin, K.Z.L. and Svensson, L.A.; U.S. Patent 3,937,838; February 10, 1976; assigned to A.B. Draco (Sweden)

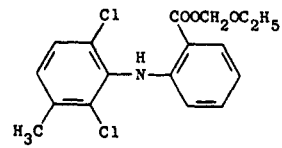
TEROFENAMATE

Therapeutic Function: Antiinflammatory, analgesic

Chemical Name: 2-[(2,6-Dichloro-3-methylphenyl)amino] benzoic acid ethoxymethyl ester

Common Name: Etoclofene

Structural Formula:



Chemical Abstracts Registry No.: 29098-15-5

Trade Name	Manufacturer	Country	Year Introduced
Etofen Ilfi	Lusofarmaco	Italy	1980

Raw Materials

N-2,6-Dichloro-m-tolylanthranilic acid
Chloromethyl ethyl ether

Manufacturing Process

10 g sodium salt of N-2,6-dichloro-m-tolylanthranilic acid, 3 ml chloromethyl ethyl ether and 80 ml dry acetone were refluxed for 12 hours on waterbath under stirring. The solid was filtered off, and the solution evaporated to dryness. The residue was dissolved in chloroform, washed with sodium carbonate solution, then with water until neutral. After drying on sodium sulfate, the solution was evaporated to dryness. The obtained product was recrystallized from 95% ethanol. Melting point 73°C to 74°C.

References

Merck Index 8992
DFU 1 (8) 421 (1976)
I.N. p. 927
Manghisi, E.; U.S. Patent 3,642,864; February 15, 1972; assigned to Istituto Luso Farmaco D'Italia S.R.L. (Italy)

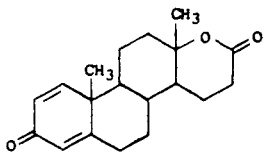
TESTOLACTONE

Therapeutic Function: Cancer chemotherapy

Chemical Name: D-homo-17-α-oxaandrosta-1,4-diene-3,17-dione

Common Name: 1-dehydrotestololactone

Structural Formula:



Chemical Abstracts Registry No.: 968-93-4

Trade Name	Manufacturer	Country	Year Introduced
Fludestrin	Heyden	W. Germany	1968
Teslac	Squibb	U.S.	1969

Raw Materials

Bacterium *Cylindrocarpon radicola*
Corn steep liquor
Brown sugar

Manufacturing Process

(a) Fermentation: A medium of the following composition is prepared: 3.0 grams corn-steep liquor solids; 3.0 grams $NH_4H_2PO_4$; 2.5 grams $CaCO_3$; 2.2 grams soybean oil; 0.5 gram progesterone and distilled water to make 1 liter. The medium is adjusted to pH 7.0±0.1. Then, 100 ml portions of the medium are distributed in 500 ml Erlenmeyer flasks and the flasks plugged with cotton and sterilized in the usual manner (i.e., by autoclaving for 30 minutes at 120°C). When cool, each of the flasks is inoculated with 5 to 10% of a vegetative inoculum of *Cylindrocarpon radicola* [the vegetative inoculum being grown from stock cultures (lyophilized vial or agar slant) for 48 to 72 hours in a medium of the following composition: 15 grams cornsteep liquor; 10 grams brown sugar; 6 grams $NaNO_3$; 0.001 gram $ZnSO_4$; 1.5 grams KH_2PO_4; 0.5 gram $MgSO_4 \cdot 7H_2O$; 5 grams $CaCO_3$; 2 grams lard oil; and distilled water to make 1 liter].

The flasks are then placed on a reciprocating shaker (120 one and one-half inch cycles per minute) and mechanically shaken at 25°C for 3 days. The contents of the flasks are then pooled and, after the pH of the culture is adjusted to about 4±0.2 with sulfuric acid, filtered through Seitz filter pads to separate the mycelium from the fermented medium.

(b) Extraction: 40 liters of the culture filtrate obtained in (a) is extracted with 40 liters chloroform in an extractor (e.g., Podbelniak, U.S. Patent 2,530,886, or improvements thereon) and the filtered chloroform extract is evaporated to dryness in vacuo. The residue (11.1 grams) is taken up in 200 ml of 80% aqueous methanol, and the resulting solution is extracted four times with 100 ml portions of hexane. The 80% aqueous methanol solution is then concentrated in vacuo until crystals appear; and, after cooling at 0°C for several (usually about 3 to 4) hours, the crystals formed are recovered by filtration. About 2.9 grams 1-dehydrotestololactone (MP 217° to 217.5°C) are thus obtained. Concentration of the mother liquors yields additionally about 6.0 grams of the lactone. Recrystallization from acetone yields a purified 1-dehydrotestololactone having a melting point of 218° to 219°C.

References

Merck Index 8999
Kleeman & Engel p. 860
PDR p. 1768
OCDS Vol. 2 p. 160 (1980)
I.N. p. 928
REM p. 1000
Fried, J. and Thoma, R.W.; U.S. Patent 2,744,120; May 1, 1956; assigned to Olin Mathieson Chemical Corporation

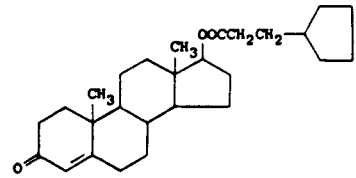
TESTOSTERONE 17β-CYPIONATE

Therapeutic Function: Androgen

Chemical Name: 17β-(3-Cyclopentyl-1-oxopropoxy)androst-4-en-3-one

Common Name: Depo-testosterone

Structural Formula:



Chemical Abstracts Registry No.: 58-20-8

Trade Name	Manufacturer	Country	Year Introduced
Depo-Testosterone	Upjohn	U.S.	1951
T-Ionate P.A.	Tutag	U.S.	1970
Andro-Cyp	Keene	U.S.	–
Andronate	Pasadena	U.S.	–
Ciclosterone	Farmigea	Italy	–
Depostomead	Spencer-Mead	U.S.	–
Depotest	Blaine	U.S.	–
Dep-Test	Sig	U.S.	–
Dep-Testosterone	Rocky Mtn.	U.S.	–
Durandro	Ascher	U.S.	–
Jectatest	Reid-Provident	U.S.	–
Malogen Cyp	O'Neal, Jones & Feldman	U.S.	–
Pertestis Dep.	Orma	Italy	–
Testomed P.A.	Medics	U.S.	–
Testorit-Dep	Gallo	Italy	–

Raw Materials

β-Cyclopentylpropionic acid
Testosterone 3-enol-ethyl ether
Acetic anhydride
Hydrogen chloride

Manufacturing Process

1 g of crude 3-enol-ethyl ether of testosterone dissolved in 3 cc of pyridine is treated with 2 cc of β-cyclopentylpropionic anhydride (obtained from the β-cyclopentylpropionic acid and acetic anhydride: boiling point 180°C/2 mm Hg). After standing at room temperature overnight the mixture is diluted with water and extracted with ether, the ethereal layer, washed with water to neutrality and dried, is evaporated by vacuum. The oily residue is taken up in petroleum ether and filtered through a layer of aluminum oxide, which is afterwards washed with a further amount of petroleum ether. The solution so filtered and purified is evaporated to dryness; the crystalline residue is recrystallized from a small amount of methanol containing a trace of pyridine: about 1 g of 3-enol-ethyl-ether of the β-cyclopentyl propionate of testosterone, melting point 86°C to 88°C. is so obtained (by further recrystallization melting point 90°C to 91°C). This product (that may be employed either in the crystalline state, or in the oily one, that is, before the purification by filtration through aluminum oxide) by treatment with a small amount of hydrochloric acid in acetone solution yields the β-cyclopentyl propionate of testosterone, melting point 99°C to 101°C (recrystallized from methanol).

References

Merck Index 9002
Kleeman & Engel p. 861
PDR pp. 950, 1033, 1841
OCDS Vol. 1 p. 172 (1977)

I.N. p. 929
REM p. 1001
Ercoli, A. and de Ruggieri, P.; U.S. Patent 2,742,485; April 17, 1956; assigned to Francesco Vismara Societa per Azioni & A. Ercoli (Italy)

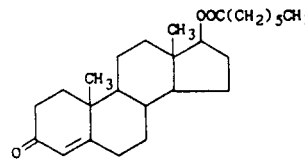
TESTOSTERONE ENANTHATE

Therapeutic Function: Androgen

Chemical Name: 17β-[(1-oxoheptyl)oxy] androst-4-en-3-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 315-37-7

Trade Name	Manufacturer	Country	Year Introduced
Delatestryl	Squibb	U.S.	1954
Reposo-TMD	Canfield	U.S.	1961
Testate	Savage	U.S.	1970
Testostroval PA	Tutag	U.S.	1970
Androtardyl	S.E.P.P.S.	France	–
Andryl	Keene	U.S.	–
Arderone	Buring-Arden	U.S.	–
Atlatest	I.C.I.	U.S.	–
Deladumon	Squibb	U.S.	–
Delatest	Dunhall	U.S.	–
Dura-Testate	Ries	U.S.	–
Duratesterone	Myers-Carter	U.S.	–
Enarmon	Teikoku Zoki	Japan	–
Everone	Hyrex	U.S.	–
Malogen LA	Fellows	U.S.	–
Malogex	Stickley	Canada	–
Primoteston	Schering	W. Germany	–
Reprosteron	Spencer-Mead	U.S.	–
Repro Testro Med	Medics	U.S.	–
Retandros	Rocky Mtn.	U.S.	–
Span-Test	Scrip	U.S.	–
Tesone	Sig	U.S.	–
Testanate	Kenyon	U.S.	–
Testinon	Mochida	Japan	–
Testisan Depo	I.E. Kimya Evi	Turkey	–
Testo-Enant	Geymonat Sud	Italy	–
Testone	Ortega	U.S.	–
Testrin	Pasadena	U.S.	–
Testoviron	Schering	W. Germany	–
Testrone	N. Amer. Pharm.	U.S.	–

Raw Materials

Oenanthic acid
Testosterone

Manufacturing Process

A mixture of testosterone, pyridine and oenanthic acid anhydride is heated for 1½ hours to 125°C. The cooled reaction mixture is decomposed with water while stirring and cooling. After prolonged standing at a temperature below room temperature, the whole is extracted with ether and the ethereal solution is washed consecutively with dilute sulfuric acid, water, 5% sodium hydroxide solution, and again with water. The crude ester remaining on evaporation of the dried ether solution, after recrystallization from pentane, melts at 36° to 37.5°C.

References

Merck Index 9003
Kleeman & Engel p. 862
PDR pp. 1033, 1604
I.N. p. 929
REM p. 1001
Junkmann, K., Kathol, J. and Richter, H.; U.S. Patent 2,840,508; June 24, 1958; assigned to Schering AG, Germany

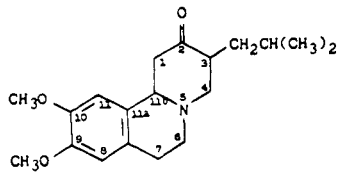
TETRABENAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo-[a] quinolizin-2-one

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 58-46-8

Trade Name	Manufacturer	Country	Year Introduced
Nitoman	Roche	U.K.	1960

Raw Materials

1-Carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline
Isobutyl malonic acid dimethyl ester
Paraformaldehyde
Sodium
Ethanol
Hydrogen chloride

Manufacturing Process

280 grams of 1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 150 grams of mono-isobutylmalonic acid dimethyl ester and 35 grams of paraformaldehyde were refluxed for 24 hours in 1,000 ml of methanol. Upon cooling, 1-carbethoxymethyl-2-(2,2-dicarbomethoxy-4-methyl-n-pentyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline crystallized; MP after recrystallization from methanol, 94° to 96°C. The latter was subjected to Dieckmann cyclization, hydrolysis and decarboxylation in the following manner.

28 grams of sodium was dissolved in 650 ml of absolute ethanol, the solution was concentrated to dryness, and the residue was mixed with 3,600 ml of toluene and 451 grams of the intermediate prepared above. The mixture was heated, and the methanol formed by condensation was distilled off until the boiling point of toluene was reached. The mixture was thereupon refluxed for 2 hours, and then it was concentrated to dryness. The residue was dissolved in 5,200 ml of 3 N hydrochloric acid and heated for 14 hours at 120°C, thereby effecting hydrolysis and decarboxylation. The mixture was cooled, washed with diethyl ether, decolorized with carbon, made alkaline and taken up in diethyl ether. The process yields 2-oxo-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-benzo[a]-quinolizine; MP after recrystallization from diisopropyl ether, 126° to 128°C.

References

Merck Index 9009
OCDS Vol. 1 p. 350 (1977)
I.N. p. 931
Brossi, A., Schnider, O. and Walter, M.; U.S. Patent 2,830,993; April 15, 1958; assigned to Hoffmann-La Roche, Inc.

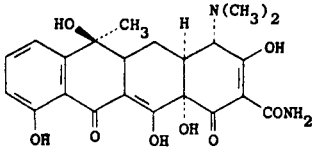
TETRACYCLINE

Therapeutic Function: Antibacterial

Chemical Name: 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide

Common Name: Deschlorobiomycin; omegamycin

Structural Formula:



Chemical Abstracts Registry No.: 60-54-8

Trade Name	Manufacturer	Country	Year Introduced
Tetracyn	Pfizer	U.S.	1953
Achromycin	Lederle	U.S.	1953
Polycycline	Bristol	U.S.	1954
Panmycin	Upjohn	U.S.	1955
Cancycline	Canfield	U.S.	1964
Abricycline	Farmakhim	Bulgaria	–
Biotetra	I.E. Kimya Evi	Turkey	–

Trade Name	Manufacturer	Country	Year Introduced
Copharlan	Cophar	Switz.	–
Economycin	D.D.S.A.	U.K.	–
Mervacycline	Byk	Neth.	–
Mysteclin	Squibb	U.S.	–
Pediatetracycline	Theranol	France	–
Pervasol	Poen	Argentina	–
Sanbiotetra	Santos	Spain	–
SK-Tetracycline	SKF	U.S.	–
Sumycin	Squibb	U.S.	–
Teclinazets	Miluy	Spain	–
Tetra-Co	Coastal	U.S.	–
Tetramig	Inava	France	–
Tetra-Proter	Proter	Italy	–

Raw Materials

Chlortetracycline
Hydrogen
Bacterium *Streptomyces aureofaciens*

Manufacturing Process

Tetracycline is usually prepared by the catalytic dechlorination of chlortetracycline as described in U.S. Patents 2,699,054 and 3,005,023, or obtained directly by fermentation of *Streptomyces aureofaciens* or *Streptomyces viridifaciens* according to U.S. Patents 2,712,517, 2,734,018, 2,886,595 and 3,019,173. The purification of tetracycline produced by either route is described in U.S. Patent 3,301,899.

The production of tetracycline by catalytic dechlorination is described in U.S. Patent 2,699,054 as follows: Pure chlortetracycline (4.8 grams) was suspended in 100 ml of methanol and sufficient anhydrous dioxane was added to completely dissolve the product. To the solution was added 0.5 gram of 5% palladium-on-charcoal catalyst. The mixture was placed in a conventional hydrogenation apparatus and subjected to a pressure of 50 psi of hydrogen while being agitated.

After the initial drop in pressure due to the absorption of gas by the catalyst and the solvent, there was a steady drop in pressure due to the hydrogenation of the antibiotic. After approximately 1 mol of hydrogen had been absorbed, no further reaction was observed. This occurred after about 2 hours. The catalyst was filtered and washed with boiling methanol and boiling dioxane. The solution gave a positive test for chloride ion when treated with silver nitrate solution. It also possessed a strongly acidic reaction demonstrating the release of the nonionic chlorine in the form of hydrogen chloride. A bioassay of the crude product in solution indicated a potency of approximately 580 μg/mg with oxytetracycline as the standard at a potency of 1,000 μg/mg. The solution was concentrated under vacuum at room temperature and the residual liquid was dried from the frozen state under vacuum. 3.1 grams of bright yellow amorphous tetracycline hydrochloride was obtained.

This product may be converted to tetracycline per se by redissolving it in water, carefully neutralizing it to pH 4.5 with dilute sodium hydroxide, and recovering the product by drying the solution.

References

Merck Index 9021
Kleeman & Engel p. 864
PDR pp. 996, 1391, 1723, 1752, 1767
OCDS Vol. 1 p. 212 (1977)
I.N. p. 932
REM p. 1207

Conover, L.H.; U.S. Patent 2,699,054; January 11, 1955
Gourevitch, A. and Lein, J.; U.S. Patent 2,712,517; July 5, 1955; assigned to Bristol Laboratories Inc.
Minieri, P.P., Sokol, H. and Firman, M.C.; U.S. Patent 2,734,018; February 7, 1956; assigned to American Cyanamid Company
Heinemann, B. and Hooper, I.R.; U.S. Patent 2,886,595; May 12, 1959; assigned to Bristol Laboratories Inc.
Miller, P.A.; U.S. Patent 3,005,023; October 17, 1961; assigned to American Cyanamid Company
Arishima, M. and Sekizawa, Y.; U.S. Patent 3,019,173; January 30, 1962; assigned to American Cyanamid Company
Kaplan, M.A. and Granatek, A.P.; U.S. Patent 3,301,899; January 31, 1967; assigned to Bristol-Myers Company

TETRACYCLINE PHOSPHATE COMPLEX

Therapeutic Function: Antibacterial

Chemical Name: Tetracycline phosphate complex; see tetracycline for chemical name

Common Name: –

Structural Formula: See tetracycline for formula of base

Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Tetrex	Bristol	U.S.	1956
Sumycin	Squibb	U.S.	1957
Panmycin Phos	Upjohn	U.S.	1957
Austrastaph	C.S.L.	Australia	–
Binicap	S.A.M.	Italy	–
Biocheclina	Wolner	Spain	–
Bristaciclina Retard	Antibioticos	Spain	–
Conciclina	Lusofarmaco	Italy	–
Devacyclin	Deva	Turkey	–
Fusfosiklin	T.E.M.S.	Turkey	–
Hexacycline	Diamant	France	–
Tetraksilin	Atabay	Turkey	–
Tetralet	Fako	Turkey	–
Tetramin	Efeyn	Spain	–
Tetrazetas Retard	Miluy	Spain	–
Upcyclin	Cophar	Switz.	–

Raw Materials

Tetracycline
Phosphorus pentoxide

Manufacturing Process

In a 500-ml round-bottomed flask equipped with stirrer, condenser and thermometer was placed 7.1 grams (0.05 mol) P_2O_5 which was immediately covered with 100 ml of chloroform. To the mixture was added with stirring 0.9 ml (0.05 mol) of distilled water. In a

few minutes, a lower oily layer appeared, which was believed to be freshly formed metaphosphoric acid resulting from the action of the P_2O_5 with an equimolar amount of water. To this mixture was added 100 ml of methanol and on continued stirring, the lower oily layer disappeared in the methanol forming a complete pale yellowish-green colored solution.

An additional 50 ml of methanol was added to the flask and then 22.2 grams (0.05 mol) of tetracycline, neutral form, was added portionwise intermittently with another 50 ml of methanol. A clear solution was maintained throughout the addition of the tetracycline. After addition of all of the tetracycline, the solution was a deep orange color and the temperature in the reaction flask was 35°C.

One hour after addition of the tetracycline, the clear reaction solution was poured into 1,500 ml of chloroform. A yellow product separated and was collected on a coarse sintered glass filter and air dried. The tetracycline-metaphosphoric acid complex weighed about 10 grams, contained 7.34% of phosphorus and had a bioassay of 634 gammas per milligram. Solubility in water is 750 mg/ml.

References

Merck Index 9021
I.N. p. 933
REM p. 1208
Sieger, G.M. Jr. and Weidenheimer, J.F.; U.S. Patent 3,053,892; September 11, 1962; assigned to American Cyanamid Company

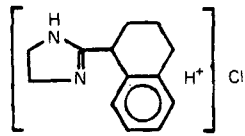
TETRAHYDROZOLINE HYDROCHLORIDE

Therapeutic Function: Nasal decongestant, eye preparation

Chemical Name: 4,5-Dihydro-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-1H-imidazole hydrochloride

Common Name: Tetryzoline HCl

Structural Formula:



Chemical Abstracts Registry No.: 522-48-5; 84-22-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tyzine	Pfizer	U.S.	1954
Visine	Leeming	U.S.	1958
Constrilia	P.O.S.	France	1979
Azolin	*Fischer*	*Israel*	–
Burnil	Kurtsan	Turkey	–
Collyrium	Wyeth	U.S.	–
Ischemol	Farmila	Italy	–
Murine	Ross	U.S.	–
Narbel	Chugai	Japan	–
Nasin	Abic	Israel	–
Oftan-Starine	Star	Finland	–

Trade Name	Manufacturer	Country	Year Introduced
Rhinopront	Mack	W. Germany	–
Stilla	Abic	Israel	–
Tinarhinin	VEB Berlin Chemie	E. Germany	–
Typinal	Ikapharm	Israel	–
Yxin	Pfizer	W. Germany	–

Raw Materials

1,2,3,4-Tetrahydro-α-naphthoic acid
Ethylenediamine
Hydrogen chloride

Manufacturing Process

A mixture of 540 grams (9.0 mols) of ethylenediamine, 270 grams (1.53 mols) of 1,2,3,4-tetrahydro-alpha-naphthoic acid, and 360 ml (4.32 mols) of concentrated hydrochloric acid was introduced into a two-liter, three-necked flask fitted with a thermometer, stirrer, and distillation takeoff. The mixture was distilled under a pressure of about 20 mm of mercury absolute until the temperature rose to 210°C. Thereafter, heating was continued under atmospheric pressure and when the temperature reached about 260°C, an exothermic reaction was initiated. The heat was then adjusted to maintain a reaction temperature of 275° to 280°C for 45 minutes and the mixture thereafter cooled to room temperature.

900 ml of 4 N hydrochloric acid was added and the aqueous layer stirred with warming until a clear, brown solution resulted. This brown solution was made strongly alkaline with sodium hydroxide. The oil that separated solidified and was collected on a filter leaving filtrate A. The solid was dissolved in 370 ml of alcohol with warming, and the solution was treated with 130 ml of concentrated hydrochloric acid with stirring and cooling. This acidified mixture was diluted with 300 ml of ether and chilled. The solid salt was collected and dried and the filtrate concentrated to approximately 300 ml, diluted with 300 ml of ether and the salt which separated collected and dried.

Filtrate A was extracted with ether, dried, acidified with alcoholic hydrogen chloride, and the salt which separated was collected and dried. There was thus obtained, when all the salt had been combined, 250 grams (69.3% of the theoretical yield) of 2-(1,2,3,4-tetrahydro-1-naphthyl)imidazoline hydrochloride, melting at 256° to 257°C.

References

Merck Index 9042
Kleeman & Engel p. 867
PDR pp. 974, 1555, 1945
OCDS Vol. 1 p. 242 (1977)
I.N. p. 936
REM p. 890
Synerholm, M.E., Jules, L.H. and Sahyun, M.; U.S. Patent 2,731,471; January 17, 1956; assigned to Sahyun Laboratories
Gardocki, J.F., Hutcheon, D.E., Lanbach, G.D. and P'an, S.Y.; U.S. Patent 2,842,478; July 8, 1958; assigned to Chas. Pfizer & Co., Inc.

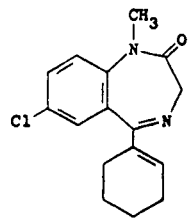
TETRAZEPAM

Therapeutic Function: Muscle relaxant

Chemical Name: 7-chloro-5-(1-cyclohexen-1-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 10379-14-3

Trade Name	Manufacturer	Country	Year Introduced
Myolastan	Clin-Comar	France	1969
Musaril	Mack-Midy	W. Germany	1980

Raw Materials

7-Chloro-5-cyclohexyl-2-oxo-2,3-dihydro-1H-benzo(f)diazepine-1,4
Sodium hypochlorite
Lithium carbonate
Sodium methylate
Methyl iodide

Manufacturing Process

1,7-Dichloro-5-Cyclohexyl-2-Oxo-2,3-Dihydro 1H-Benzo(f)-Diazepine-1,4: (a) Process Using Sodium Hypochlorite – 40 ml of a solution of sodium hypochlorite of 14.5 British chlorometric degrees are added to a suspension of 5.4 grams of 7-chloro-5-cyclohexyl-2-oxo-2,3-dihydro 1H-benzo(f)diazepine-1,4 in 80 ml of methylene chloride. The mixture is stirred at room temperature for 15 minutes; the solid dissolves rapidly. The organic layer is decanted, washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure without exceeding a temperature of 30°C. The residue is taken up in a little diisopropyl ether and the crystals which form are dried. They are recrystallized as rapidly as possible from ethyl acetate. Colorless crystals are obtained (3.9 grams; yield, 85%); MP_k = 163°C, with decomposition.

(b) Process Using Tertiary-Butyl Hypochlorite – 1.2 grams of tertiary-butyl hypochlorite are added to a suspension of 2.7 grams of 7-chloro-5-cyclohexyl-2-oxo-2,3-dihydro 1H-benzo(f)diazepine-1,4 in 20 ml of methylene chloride and the mixture is stirred and at the same time cooled in a water bath for 30 minutes. The solid dissolves in about 15 minutes. The product is evaporated to dryness under reduced pressure at a temperature below 40°C. The residue is taken up in diisopropyl ether and the crystals which separate are dried. Colorless crystals are obtained (2.8 grams; yield, 98%); MP_k = 161° to 162°C, with decomposition, according to U.S. Patent 3,551,412.

7-Chloro-5-(1'-Chlorocyclohexyl)-2-Oxo-2,3-Dihydro 1H-Benzo(f)Diazepine-1,4: A solution of 117 grams of the compound prepared above in 450 ml ethyl acetate is heated under reflux until a precipitate begins to form. From then onwards reflux is continued until a negative reaction is obtained when the reaction mixture is tested with a solution of sodium iodide in acetone. The reaction mixture is left to cool and the solid which separates is dried. Colorless crystals are obtained (76 grams), MP_k = 194° to 195°C, with decomposition. A second portion (14 grams) is isolated by concentrating the mother liquor, MP_k = 194° to 195°C, with decomposition. The total yield is 77%. The melting point is raised to 196° to 197°C by recrystallization from ethyl acetate.

7-Chloro-5-(1'-Cyclohexenyl)-2-Oxo-2,3-Dihydro 1H-Benzo(f)Diazepine-1,4: 68 grams of 7-chloro-5-(1'-chlorocyclohexyl)-2-oxo-2,3-dihydro 1H-benzo(f)diazepine-1,4, 34 grams of lithium carbonate and 17 grams of lithium bromide and 340 ml of anhydrous dimethylformamide are placed in a three-necked flask equipped with a mechanical stirrer, immersion thermometer and a reflux condenser connected with a bubble counter.

The reaction mixture is gradually heated, with stirring, until evolution of carbon dioxide commences (about 100°C) and the temperature is maintained thereat until the reaction ceases. The temperature is then raised to 110°C and held thereat for 15 minutes.

The reaction mixture is allowed to cool and the mineral salts separated and dried. The solvent is evaporated under reduced pressure and the residue dissolved in water. It is allowed to crystallize, dehydrated, dried and then recrystallized from ethyl acetate. The product is yellowish crystals (47.5 grams; yield, 80%); MP_k = 207° to 208°C.

7-Chloro-5-(1'-Cyclohexenyl)-1-Methyl-2-Oxo-2,3-Dihydro 1H-Benzo(f)Diazepine-1,4: 9.7 grams of sodium methylate are added to a solution of 16.5 grams of 7-chloro-5-(1'-cyclohexenyl)-2-oxo-2,3-dihydro 1H-benzo(f)diazepine-1,4 dissolved in 120 ml of dry dimethylformamide and the mixture stirred for one-half hour. The reaction mixture is cooled in a water bath and a solution of 33.8 grams of methyl iodide dissolved in 35 ml of anhydrous dimethylformamide is then slowly added with stirring. The solution becomes dark brown in color and a precipitate forms. It is stirred for 2 hours, then diluted with a large volume of water and extracted with ethyl acetate. The ethyl acetate solution is washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue is crystallized from a small volume of ethyl acetate. Brownish yellow crystals are obtained (9 grams; yield, 52%), MP_k = 144°C.

References

Merck Index 9065
Kleeman & Engel p. 865
DOT 6 (4) 148 (1970)
I.N. p. 936
Berger, L. and Sternbach, L.H.; U.S. Patent 3,268,586; August 23, 1966; assigned to Hoffmann-La Roche Inc.
Schmitt, J.; U.S. Patent 3,426,014; February 4, 1969; assigned to Etablissements Clin-Byla, France
Schmitt, J.; U.S. Patent 3,551,412; December 29, 1970; assigned to Etablissements Clin-Byla, France

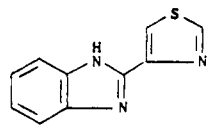
THIABENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: 2-(4-thiazolyl)-1H-benzimidazole

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 148-79-8

Trade Name	Manufacturer	Country	Year Introduced
Mintezol	MSD	U.S.	1967
Mintezol	MSD	U.K.	1968
Mintezol	MSD-Chibret	France	1969
Minzolum	Sharp & Dohme	W. Germany	1970

Raw Materials

Thiazole-4-carboxylic acid
Thionyl chloride
Zinc
o-Nitroaniline
Hydrogen chloride

Manufacturing Process

6.5 grams of thiazole-4-carboxylic acid is stirred with 5.9 grams of thionyl chloride in 20 ml xylene for 10 hours at room temperature to form 4-thiazolyl acid chloride. 1.3 grams of 4-thiazolyl acid chloride and 1.3 grams of o-nitroaniline are then stirred together in 3.5 ml of pyridine at room temperature for about 12 hours. At the end of this time, the mixture is quenched in ice water and the solid nitroanilide recovered by filtration and washed with dilute sodium carbonate solution. The solid is suspended in 15 ml of glacial acetic acid, and 8 ml of 6 N hydrochloric acid added to the suspension. 6 grams of zinc dust is added in small portions to the acetic mixture. After the zinc addition is complete, and the reaction is essentially finished (by visual observation), the reaction mixture is filtered and the filtrate neutralized with concentrated ammonium hydroxide to precipitate 2-(4'-thiazolyl)-benzimidazole. The product is purified by recrystallization from ethyl acetate, according to U.S. Patent 3,274,207.

References

Merck Index 9126
PDR p. 1200
OCDS Vol. 1 p. 325 (1977)
DOT 7 (5) 195 (1971)
REM p. 1237
Sarett, L.H. and Brown, H.D.; U.S. Patent 3,017,415; January 16, 1962; assigned to Merck & Co., Inc.
Kaufman, A. and Wildman, G.T.; U.S. Patent 3,262,939; July 26, 1966; assigned to Merck & Co., Inc.
Kollonitsch, J.; U.S. Patent 3,274,207; September 20, 1966; assigned to Merck & Co., Inc.
Jones, R.E. and Gal, G.; U.S. Patent 3,274,208; September 20, 1966; assigned to Merck & Co., Inc.

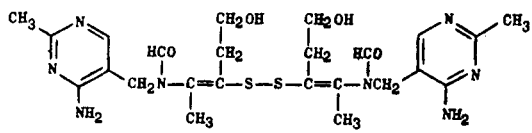
THIAMINE DISULFIDE

Therapeutic Function: Enzyme cofactor vitamin

Chemical Name: N,N'-[dithiobis[2-(2-hydroxyethyl)-1-methylvinylene]]bis[N-[(4-amino-2-methyl-5-pyrimidinyl)methyl] formamide]

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 67-16-3

Trade Name	Manufacturer	Country	Year Introduced
Arcalion	Servier	France	1974

Raw Materials

Thiamine
Potassium ferricyanide

Manufacturing Process

20 parts by weight of thiamin are dissolved in 25 parts of water, a cold solution of 5 parts by weight of caustic soda in 25 parts of water added and the mixture oxidized with a solution of 2.4 parts by weight of caustic soda and 20 parts by weight of potassium ferric cyanide in 80 parts of water while stirring in the cold. The liquid is then evaporated to dryness and the resulting oxidation product extracted with warm butyl alcohol.

The butyl-alcoholic solution is evaporated in vacuo and the residue dissolved with gentle heating in 25 parts by volume of methyl alcohol. 100 parts by volume of acetone are added, the solution filtered and further quantities of acetone added, whereupon crystallization sets in. Yield: 12.2 parts by weight of the pure product, having the melting point 177° to 179°C.

References

Merck Index 9130
I.N. p. 941
Warnat, K.; U.S. Patent 2,458,453; January 4, 1949; assigned to Hoffmann-La Roche Inc.

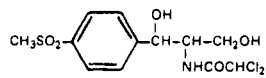
THIAMPHENICOL

Therapeutic Function: Antibacterial

Chemical Name: D-Threo-2,2-dichloro-N-[β-hydroxy-α-(hydroxymethyl)-p-methylsulfonylphenethyl] -acetamide

Common Name: Dextrosulphenidol, thiophenicol

Structural Formula:



Chemical Abstracts Registry No.: 15318-45-3

Trade Name	Manufacturer	Country	Year Introduced
Thiophenicol	Clin Midy	France	1967
Chlomic J	Kowa Shinyaku	Japan	–
Descocin	Kanto	Japan	–
Efnicol	Nichizo	Japan	–
Ericol	S.S. Pharm	Japan	–
Glitisol Orale	Zambon	Italy	–
Hyrazin	Kowa	Japan	–
Igralin	Zeria	Japan	–
Macphenicol	Nakataki	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Masatirin	Maruko	Japan	–
Namicain	Nippon Kayaku	Japan	–
Neomyson	Eisai	Japan	–
Racenicol	Kissei	Japan	–
Rigelon	Dojin	Japan	–
Rincrol	Tanabe	Japan	–
Roseramin	Takata	Japan	–
Synticol	Nisshin	Japan	–
Thiamcetin	Mochida	Japan	–
Thiamcol	Morishita	Japan	–
Thiamyson	Ohta	Japan	–
Thiancol	Kakenyaku	Japan	–
Thiofact	Showa	Japan	–
Thionicol	Mohan	Japan	–
Thiotal	Sumitomo	Japan	–
Tiozon	Mitsui	Japan	–
Unaseran-D	Isei	Japan	–
Urfamycine	Zambon	Italy	–
Urophenyl	Sanwa	Japan	–

Raw Materials

2-Acetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol
Hydrogen chloride
Ethyl dichloroacetate
Peracetic acid

Manufacturing Process

A mixture of 50 parts by weight of racemic 2-acetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol, 100 parts by weight of concentrated hydrochloric acid, and 500 parts by weight of water was warmed on a steam bath for thirty minutes. The resulting solution was cooled to about 40°C and was then made strongly alkaline by addition of 35% aqueous sodium hydroxide solution. The alkaline solution was then refrigerated. The white solid which separated from the cooled solution was collected on a filter. There was thus obtained 27 parts by weight of 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol. This product melted at 130.7°C to 131.9°C after recrystallization from methanol.

This compound was converted to the tartrate and the optical isomers were resolved.

A mixture of 1.1 g of 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol, obtained as described above and 1.6 ml of ethyl dichloroacetate was heated on a steam bath for three hours. The resulting viscous yellow oil was dissolved in 25 ml of ethylene chloride and filtered hot with charcoal, and the filtrate was allowed to cool to about 25°C. From the filtrate there separated 0.92 g of tiny white leaflets which were collected on a filter. Recrystallization of this product, which was a dextro-rotary form of 2-dichloroacetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol from nitroethane yielded the pure product, which melted at 111.6°C to 112.6°C.

7 g of the 2-dichloroacetylamino-1-(4-methylmercaptophenyl)-1,3-propanediol obtained as described above was dissolved in 30 ml of acetone. To this solution there was added dropwise with stirring 10 ml of 40% peracetic acid. The temperature during the reaction was maintained at 39°C to 45°C by cooling the reaction vessel. After stirring the mixture for two hours, it was diluted with 100 ml of water and the solution allowed to stand over the weekend in the refrigerator. The solid which separated from solution was collected on a filter, washed several times with ice water, and dried overnight at 70°C.

References

Merck Index 9140
Kleeman & Engel p. 874
OCDS Vol. 2 p. 45 (1980)
I.N. p. 942
Suter, C.M.; U.S. Patent 2,759,976; August 21, 1956; assigned to Sterling Drug, Inc.
Parke, Davis & Co.; British Patent 770,277; March 20, 1957

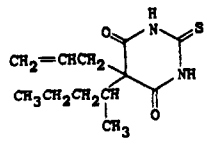
THIAMYLAL

Therapeutic Function: Anesthetic (injectable)

Chemical Name: Dihydro-5-(1-methylbutyl)-5-(2-propenyl)-2-thioxo-4,6(1H,5H)-pyrimidinedione

Common Name: Thioseconal

Structural Formula:



Chemical Abstracts Registry No.: 77-27-0

Trade Name	Manufacturer	Country	Year Introduced
Surital	Parke Davis	U.S.	1951
Citosol	Kyorin	Japan	–
Isozol	Yoshitomi	Japan	–

Raw Materials

Diethyl allyl-(1-methylbutyl)malonate
Sodium
Methanol
Thiourea

Manufacturing Process

In 450 cc of methanol is added 47 grams of sodium metal and the mixture allowed to completely react to form a methanol solution of sodium methoxide. The methanol solution of sodium methoxide is then cooled to 60°C and 68 grams of thiourea which has been thoroughly dried is added with stirring until a uniform solution is formed. Thereafter, 157 grams of diethyl allyl-(1-methylbutyl)malonate is added to the solution of the sodio derivative of thiourea at a temperature of 55°C and the condensation reaction mixture maintained at the said temperature for 24 hours. Methyl alcohol is removed under vacuum during the course of the reaction while maintaining a temperature of 55°C.

The viscous reaction mixture is then poured into 1.5 liters of ice water and agitated to form a uniform solution. The solution is treated with activated carbon and filtered. Thereafter, 80% acetic acid is added until the filtered solution remains acidic to litmus. The precipitate formed is filtered and washed thoroughly with distilled water. The product is air-dried at a temperature of 95° to 100°C for 48 hours to yield 133 grams of 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid having a melting point of 132° to 133°C and assaying at 99.5% pure, from U.S. Patent 2,876,225.

References

Merck Index 9141
Kleeman & Engel p. 875
OCDS Vol. 1 p. 274 (1977)
I.N. p. 942
REM p. 1046
Volwiler, E.H. and Tabern, D.L.; U.S. Patent 2,153,729; April 11, 1939; assigned to Abbott Laboratories
Donnison, G.H.; U.S. Patent 2,876,225; March 3, 1959; assigned to Abbott Laboratories

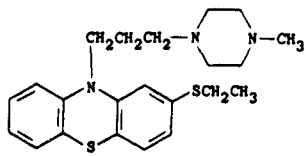
THIETHYLPERAZINE

Therapeutic Function: Antiemetic

Chemical Name: 2-(Ethylthio)-10-[3-(4-methyl-1-piperazinyl)propyl] phenothiazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 1420-55-9; 52239-63-1 (Maleate)

Trade Name	Manufacturer	Country	Year Introduced
Torecan	Boehr. Ingel.	U.S.	1961
Torecan	Sandoz	Italy	1962
Torecan	Sandoz	France	1962
Torecan	Sandoz	U.K.	1962
Torecan	Sandoz	W. Germany	1964
Toresten	Sandoz-Sankyo	Japan	–

Raw Materials

3-Ethylmercapto-phenothiazine
1-Methyl-4-(3'-chloropropyl-1')-piperazine
Sodium amide

Manufacturing Process

26.1 parts of 3-ethylmercapto-phenothiazine (melting point 95°C to 97°C), 4.7 parts of finely pulverized sodium amide and 120 parts by volume of absolute xylene are heated to boiling for two hours, under reflux and while stirring the reaction mixture, at an oil-bath temperature of 180°C. Without interrupting the heating, a solution of 20.0 parts of 1-methyl-4-(3'-chloropropyl-1')-piperazine (boiling point 95°C to 97°C at a pressure of 10 mm Hg) in 20 parts by volume of xylene is added dropwise in the course of 1½ hours. After heating 3 more hours, the reaction mixture is cooled and 10.0 parts of ammonium chloride added; the mixture is then shaken out three times, using 50 parts by volume of water each time. The xylene solution is extracted with 250 parts by volume of aqueous tartaric acid of 15% strength, after which the tartaric acid extract is washed with 80 parts by volume of benzene and then ren-

dered phenolphthalein-alkaline by the addition of 60 parts by volume of concentrated aqueous caustic soda solution. The base which precipitates is taken up in a total of 150 parts by volume of benzene; the benzene layer is dried over potassium carbonate and is then evaporated under reduced pressure. The residue from the evaporation is distilled in a high vacuum. After separating a preliminary distillate which passes over up to 226°C under a pressure of 0,01 mm Hg the main fraction—3-ethylmercapto-10-[3'(1''-methyl-piperazyl-4'')-propyl-1']-phenothiazine—which distills at 226°C to 228°C under the last-mentioned pressure is collected. The analytically pure base boils at 227°C under a pressure of 0.01 mm Hg and melts at 62°C to 64°C.

Upon the addition of ethanolic HCl to a solution, cooled to 0°C, of 26.38 parts of the free base in 130 parts by volume of absolute ethanol, until a Congo-acid reaction is achieved, the crystalline dihydrochloride of 3-ethylmercapto-10-[3'-(1''-methyl-piperazyl-4'')-propyl-1']-phenothiazine is precipitated. The analytically pure salt has a melting point of 214°C to 216°C (bubbles); it begins to sinter at 205°C. The dimaleate melts at 188°C to 190°C after sintering from 180°C (recrystallized from methanol).

References

Merck Index 9151
Kleeman & Engel p. 875
PDR p. 683
OCDS Vol. 1 p. 382 (1977)
DOT 9 (6) 228 (1973)
I.N. p. 943
REM p. 810
Renz, J., Bourquin, J.P., Gamboni, G. and Schwarb, G.; U.S. Patent 3,336,197; August 15, 1967; assigned to Sandoz, Ltd. (Switz.)

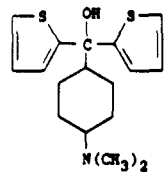
THIHEXINOL

Therapeutic Function: Anticholinergic

Chemical Name: α-[4-(Diethylamino)cyclohexyl]-α-2-thienyl-2-thiophene-methanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53626-54-3

Trade Name	Manufacturer	Country	Year Introduced
Sorboquel	Schering	U.S.	1960
Entoquel	White	U.S.	1961

Raw Materials

Ethyl-p-aminobenzoate
Formaldehyde
Magnesium
Hydrogen
2-Bromothiophene

Manufacturing Process

The requisite intermediate, ethyl 4-dimethylaminocyclohexylcarboxylate is prepared as follows: 33 g of ethyl p-aminobenzoate dissolved in 300 cc of absolute ethanol containing 16.8 cc of concentrated hydrochloric acid is hydrogenated at 50 pounds hydrogen pressure in the presence of 2 g of platinum oxide. The theoretical quantity of hydrogen is absorbed in several hours, the catalyst removed by filtration and the filtrate concentrated to dryness in vacuo. The residue is dissolved in water, made alkaline with ammonium hydroxide and extracted with chloroform. After removal of the solvent, the residual oil is distilled to yield ethyl 4-aminocyclohexylcarboxylate, boiling point 114°C to 117°C/10 mm.

A mixture of 49 g of this ester compound, 76 g of 98% formic acid and 68 ml of formalin solution is heated under reflux for 8 hours. The solvents are then removed in vacuo on the steam bath, the residue dissolved in water, made alkaline with ammonium hydroxide and extracted with chloroform. Removal of the solvent and distillation in vacuo yields ethyl 4-dimethylaminocyclohexylcarboxylate, boiling point 122°C to 125°C/10 mm.

To a solution of thienyl magnesium bromide prepared from 21.4 g of magnesium and 144 g of 2-bromothiophene are added 39.8 g of ethyl 4-dimethylaminocyclohexylcarboxylate. The mixture is allowed to warm to room temperature and stirred for an additional six hours. The reaction mixture is then decomposed with dilute ammonium chloride solution and extracted with ether. The combined ether extracts are extracted thoroughly with 10% hydrochloric acid and the acid solution made alkaline with ammonium hydroxide. The aqueous solution is extracted with chloroform which is then washed with water, dried and evaporated to a residue in vacuo. Recrystallization of the residue from hexane yields α,α^1-dithienyl-4-dimethylaminocyclohexyl carbinol, melting point 156°C to 157°C after recrystallization from benzene.

References

Merck Index 9152
I.N. p. 943
Villani, F.J.; U.S. Patent 2,764,519; September 25, 1956; assigned to Schering Corp.

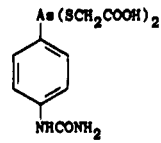
THIOCARBARSONE

Therapeutic Function: Antiamebic

Chemical Name: 2,2'-[[[4-[(Aminocarbonyl)amino] phenyl] arsinidene] bis(thio)] bis[acetic acid]

Common Name: Thio-carbamisin

Structural Formula:



Chemical Abstracts Registry No.: 120-02-5

Trade Name	Manufacturer	Country	Year Introduced
Thiocarbarsone	Lilly	U.S.	1951

Raw Materials

Thioglycolic acid
Carbarsone oxide

Manufacturing Process

121 g of thioglycolic acid and 100 g of carbarsone oxide are reacted in a solution of 128 g of sodium bicarbonate in 2 liters of water.

The mixture is heated on a steam bath for 20 minutes. The reaction mixture is then cooled and filtered to remove a small amount of insoluble material. The filtrate is diluted with about 600 cc of water and is acidified with concentrated hydrochloric acid.

On treating the reaction mixture with acid, di-(carboxymethylthio)-p-carbamidophenylarsine precipitates, and is separated by filtration and dried.

Di-(carboxymethylthio)-p-carbamidophenylarsine thus prepared was obtained as a white amorphous solid, soluble in dilute alkali. It contained about 19.85% of arsenic as compared with the calculated amount of 19.09%.

References

Merck Index 9162
I.N. p. 944
Rohrmann, E.; U.S. Patent 2,516,831; July 25, 1950; assigned to Eli Lilly & Co.

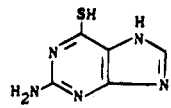
THIOGUANINE

Therapeutic Function: Cancer chemotherapy

Chemical Name: 2-aminopurine-6-thiol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 154-42-7

Trade Name	Manufacturer	Country	Year Introduced
Thioguanine Tabloid	Burroughs Wellcome	U.S.	1966
Lanvis	Wellcome	U.K.	1972
Thioguanine Wellcome	Burroughs Wellcome	Italy	1974
Thioguanin Wellcome	Burroughs Wellcome	W. Germany	1975

Raw Materials

Guanine
Phosphorus pentasulfide

Manufacturing Process

A mixture of 2.7 grams of finely divided guanine, 10 grams of pulverized phosphorus pentasulfide, 10 ml of pyridine and 100 ml of tetralin was heated at 200°C with mechani-

cal stirring for 5 hours. After cooling, the mixture was filtered and the insoluble residue treated with 150 ml of water and 50 ml of concentrated ammonium hydroxide. The ammoniacal solution was filtered, heated to boiling and acidified with acetic acid. Upon cooling, 2-amino-6-mercaptopurine precipitated as a dark yellow powder, according to U.S. Patent 2,697,709.

References

Merck Index 9177
Kleeman & Engel p. 892
PDR p. 765
OCDS Vol. 2 p. 464 (1980)
I.N. p. 954
REM p. 1153
Hitchings, G.H. and Elion, G.B.; U.S. Patent 2,697,709; December 21, 1954; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H. and Elion, G.B.; U.S. Patent 2,800,473; July 23, 1957; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H. and Elion, G.B.; U.S. Patent 2,884,667; May 5, 1959
Hitchings, G.H., Elion, G.B. and Mackay, L.E.; U.S. Patent 3,019,224; January 30, 1962; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hitchings, G.H., Elion, G.B. and Goodman, I.; U.S. Patent 3,132,144; May 5, 1964; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

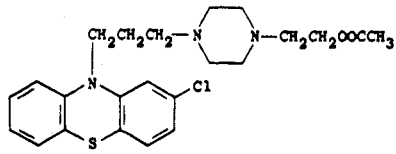
THIOPROPAZATE

Therapeutic Function: Antipsychotic

Chemical Name: 4-[3-(2-Chlorophenothiazin-10-yl)propyl] -1-piperazine-ethanol acetate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 84-06-0; 146-28-1 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Dartal	Searle	U.S.	1957
Dartalan	Searle	U.K.	–
Vesitan	Boehr. Mann.	W. Germany	–

Raw Materials

2-Chloro-10-(γ-chloropropyl)phenothiazine
Piperazine
β-Bromoethyl acetate

Manufacturing Process

A mixture of 155 parts of 2-chloro-10-(γ-chloropropyl)phenothiazine, 75 parts of sodium

iodide, 216 parts of piperazine and 2,000 parts of butanone is refluxed for 8 hours, concentrated and extracted with dilute hydrochloric acid. The extract is rendered alkaline by addition of dilute potassium carbonate and extracted with ether. This ether extract is washed with water, dried over anhydrous potassium carbonate, filtered and evaporated. Vacuum distillation at 0.1 mm pressure yields 2-chloro-10-(γ-piperazinopropyl)phenothiazine at about 214°C to 218°C.

A mixture of 50 parts of the distillate, 25.6 parts of β-bromoethyl acetate, 10.7 parts of potassium carbonate and 400 parts of toluene is stirred at reflux temperature for 16 hours. The mixture is heated with water. The organic layer is separated, washed with water and extracted with dilute hydrochloric acid. The resulting extract is washed with benzene, rendered alkaline and extracted with benzene. The resulting benzene solution is dried over anhydrous potassium carbonate, filtered and concentrated. The residue is dissolved in 300 parts of ethanol and treated with 2.2 equivalents of a 25% solution of anhydrous hydrochloric acid in 2-propanol. The resulting crystals are recrystallized from 400 parts of ethanol and 10 parts of water. The dihydrochloride of N-(β-acetoxyethyl)-N'-[γ-(2'-chloro-10'-phenothiazine)propyl] piperazine melts unsharply at about 200°C to 230°C.

References

Merck Index 9198
Kleeman & Engel p. 878
OCDS Vol. 1 p. 383 (1977)
I.N. p. 946
Cusic, J.W.; U.S. Patent 2,766,235; October 9, 1956

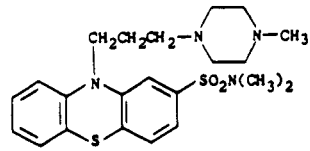
THIOPROPERAZINE

Therapeutic Function: Neuroleptic, antiemetic

Chemical Name: N,N-Dimethyl-10-[3-(4-methyl-1-piperazinyl)propyl] -phenothiazine-2-sulfonamide

Common Name: Thioperazine

Structural Formula:



Chemical Abstracts Registry No.: 316-81-4

Trade Name	Manufacturer	Country	Year Introduced
Majeptil	Specia	France	1960
Cephalmin	Shionogi	Japan	—
Mayeptil	Rhodia Pharma	W. Germany	—
Vontil	S.K.F.	U.S.	—

Raw Materials

3-Dimethylsulfamoylphenothiazine
3-(4-Methyl-1-piperazinyl)-1-chloropropane
Sodium amide

Manufacturing Process

A solution of 3-dimethylsulfamoylphenthiazine (5 g) in anhydrous xylene (100 cc) is heated under reflux for 1 hour with sodamide (0.67 g). 3-(4-methyl-1-piperazinyl)-1-chloropropane (3.2 g) in solution in anhydrous xylene (20 cc) is added and the mixture heated under reflux for 5 hours. After treatment of the reaction products, a crude oily base (2.5 g) is obtained after treatment. By the addition of a solution of fumaric acid in ethanol to an ethanolic solution of the base, 3-dimethylsulfamoyl-10-(3-4^1-methyl-1^1-piperazinylpropyl)-phenthiazine diacid fumarate (2.6 g) is obtained, melting point 182°C. The base recrystallized from ethyl acetate melts at about 140°C.

References

Merck Index 9199
Kleeman & Engel p. 879
I.N. p. 946
Soc. des Usines Chimiques Rhone-Poulenc; British Patent 814,512; June 3, 1959

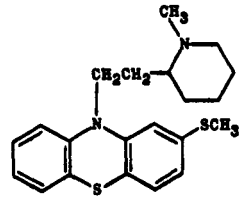
THIORIDAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)phenothiazine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 50-52-2; 130-61-0 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Mellaril	Sandoz	U.S.	1959
Mellaril	Sandoz	France	1960
Baylaril	Bay	U.S.	1983
Mellerette	Wander	Italy	—
Melleretten	Sandoz	W. Germany	—
Novoridazide	Novopharm	Canada	—
Orsanil	Orion	Finland	—
Ridazin	Taro	Israel	—
Stalleril	Pharmacal	Finland	—
Thioril	I.C.N.	Canada	—

Raw Materials

m-Methylmercaptoaniline
Sulfur
2-(N-methylpiperidyl-2')-1-chloroethane
Potassium o-chlorobenzoate
Iodine
Sodium amide

Manufacturing Process

N-(m-methylmercapto-phenyl)-aniline (MP 59° to 61°C) is prepared by condensing m-methylmercapto-aniline (BP 163° to 165°C/16 mm Hg) with the potassium salt of o-chloro-benzoic acid and decarboxylating the resultant N-(m-methylmercapto-phenyl)-anthranilic acid (MP 139° to 141°C) by heating, and then distilling.

9.87 parts of N-(m-methylmercapto-phenyl)-aniline are heated with 2.93 parts of sulfur and 0.15 part of powdered iodine for 15 minutes in a bath at about 160°C. Upon termination of the ensuing evolution of hydrogen sulfide, animal charcoal is added to the reaction mixture and recrystallization carried out first from 40 parts by volume of chlorobenzene, and then from 25 to 30 parts by volume of benzene at the boiling temperature. The obtained citron-yellow 3-methylmercapto-phenothiazine has a MP of 138° to 140°C.

17.82 parts of 2-methylmercapto-phenothiazine, 3.4 parts of finely pulverized sodamide and 80 parts by volume of absolute xylene are heated to boiling for two hours at a bath temperature of 180°C under a reflux condenser and while stirring the reaction mixture. Without interrupting the heating, a solution of 13.2 parts of 2-(N-methyl-piperidyl-2')-1-chloro-ethane in 40 parts by volume of absolute xylene is then added dropwise in the course of 1½ hours. After further heating for 3 hours, the reaction mixture is cooled and, after the addition of 5 parts of ammonium chloride, is shaken three times with water, using 25 parts by volume each time. The xylene solution is extracted once with 35 parts by volume of 3 normal acetic acid and then three times, each time with 15 parts by volume of the said acid, after which the acetic acid extract is washed with 60 parts by volume of ether and is then made phenolphthalein-alkaline by means of 25 parts by volume of concentrated aqueous caustic soda solution.

The precipitated oily base is taken up in a total of 100 parts by volume of benzene. The benzene layer, dried over potassium carbonate, is filtered and then evaporated under reduced pressure. The residue from the evaporation is distilled in a high vacuum; after separating a preliminary distillate which passes over up to 228°C under a pressure of 0.92 mm Hg, the principal fraction, 2-methylmercapto-10-[2'-(N-methyl-piperidyl-2")-ethyl-1']-phenothiazine, which distills over at 228° to 232°C under the last-mentioned pressure, is collected. The analytically pure base has a BP of 230°C/0.02 mm Hg.

References

Merck Index 9202
Kleeman & Engel p. 879
PDR pp. 1586, 1606
OCDS Vol. 1 p. 389 (1977)
DOT 9 (6) 227 (1973)
I.N. p. 946
REM p. 1090
Renz, J., Bourquin, J.P., Gamboni, G. and Schwarb, G.; U.S. Patent 3,239,514; March 8, 1966; assigned to Sandoz Ltd., Switzerland

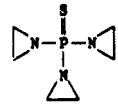
THIOTEPA

Therapeutic Function: Antineoplastic

Chemical Name: 1,1',1"-Phosphionothioylidynetrisaziridine

Common Name: Triethylenethiophosphoramide

Structural Formula:



Chemical Abstracts Registry No.: 52-24-4

Trade Name	Manufacturer	Country	Year Introduced
Thio-Tepa	Lederle	U.S.	1959
Onca-Tiotepa	Simes	Italy	–
Tespamin	Somitomo	Japan	–

Raw Materials

Ethyleneimine
Thiophosphoryl chloride

Manufacturing Process

A solution of 30.3 parts of triethylamine and 12.9 parts of ethylenimine in 180 parts of dry benzene is treated with a solution of 16.9 parts of thiophosphoryl chloride in 90 parts of dry benzene at 5°C to 10°C. Triethylamine hydrochloride is filtered off. The benzene solvent is distilled from the filtrate under reduced pressure and the resulting crude product is recrystallized from petroleum ether. The N,N',N''-triethylenethiophosphoramide had a melting point of 51.5°C.

References

Merck Index 9484
Kleeman & Engel p. 880
PDR p. 1030
I.N. p. 946
REM p. 1156
Kun, E. and Seeger, D.R.; U.S. Patent 2,670,347; February 23, 1954; assigned to American Cyanamid Co.

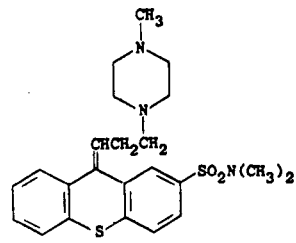
THIOTHIXENE

Therapeutic Function: Tranquilizer

Chemical Name: (Z)-N,N-dimethyl-9-[3-(4-methyl-1-piperazinyl)propylidene] thioxanthene-2-sulfonamide

Common Name: Tiotixen

Structural Formula:



Chemical Abstracts Registry No.: 3313-26-6

Trade Name	Manufacturer	Country	Year Introduced
Navane	Roerig	U.S.	1967
Navane	Pfizer	U.K.	1967
Orbinamon	Pfizer	W. Germany	1968
Navane	Pfizer Taito	Japan	1970
Navane	Pfizer	Italy	1971

Raw Materials

Thioxanthene
Thionyl chloride
n-Butyllithium
Paraformaldehyde
Sodium borohydride
Chlorosulfonic acid
Dimethylamine
Methyl acetate
1-Methylpiperazine
Phosphorus oxychloride

Manufacturing Process

Sodium Thioxanthene-2-Sulfonate: A solution of thioxanthene (32.2 grams, 0.160 mol) in 160 ml of chloroform was cooled to 0°C and chlorosulfonic acid (12.4 ml, 0.190 mol) added as rapidly as possible while maintaining the internal temperature below 10°C. After the addition was complete, the reaction mixture was allowed to approach room temperature during 30 minutes, then refluxed for an additional 20 minutes. The deep red solution was poured onto 100 grams of crushed ice and to convert the sulfonic acid to its sodium salt there was added 20 grams of sodium chloride. After filtering the slurry through a sintered glass funnel, the filter cake was washed with 50 ml of chloroform and 50 ml of 20% sodium chloride solution.

The crude sulfonate product was digested in 1,500 ml of boiling water, and filtered at the boiling point. Crystallization was allowed to proceed overnight at 4°C and after filtration and vacuum drying at 100°C, 33.3 grams (69%) of glistening, colorless plates were obtained.

2-Dimethylsulfamylthioxanthene: To a slurry of dry sodium thioxanthene-2-sulfonate (33.3 grams, 0.111 mol) in 50 ml of N,N-dimethylformamide was added thionyl chloride (14.3 grams, 0.122 mol) in divided portions. An exothermic reaction ensued with complete dissolution being effected in minutes. Treatment of the reaction mixture with crushed ice precipitated a gum which crystallized after a short period of stirring. The sulfonyl chloride was filtered, washed with water, and stirred with 100 ml of liquid dimethylamine. After allowing the mixture to evaporate to dryness, water was added and the sulfonamide filtered, washed with water, and dried in vacuo. The crude product (32.5 grams, 96%) obtained melts at 163.5° to 165°C. One crystallization from ethanol chloroform yielded an analytical sample, MP 164.5 to 166.5°C.

9-Acetyl-2-Dimethylsulfamylthioxanthene: A suspension of 2-dimethylsulfamylthioxanthene (12.22 grams, 0.04 mol) in 60 ml of dimethoxymethane is cooled to 0°C and 17.2 ml of a 2.91 M solution of n-butyl lithium in heptane is added slowly in a nitrogen atmosphere while the temperature is maintained below 10°C. After an additional 10 minutes of stirring, the cooling bath is removed and a solution of 2.96 grams of methyl acetate in 20 ml of dimethoxyethane is added during ½ hour and then the mixture is stirred at 25°C for an additional 3 hours. The reaction mixture is then treated with 60 ml of ethyl acetate and with 60 ml of a 10% aqueous ammonium chloride solution. The layers are separated and the ethyl acetate layer is washed once with water (25 ml) and then the solvent is removed by distillation.

The product is purified by the method of Teitelbaum, *J. Org. Chem.*, 23, 646 (1958). The gummy residue is treated with 7.8 grams of Girard's "T" reagent, a commercially available (carboxymethyl) trimethylammonium chloride hydrazide which can be prepared by the method described by Girard in *Organic Syntheses,* collective volume II, page 85

(1943), 0.2 grams of a methacrylic-carboxylic cation exchange resin of 20 to 50 mesh particle size, such as Amberlite IRC-50 (Rohm & Haas Co.) and 20 ml of ethanol. The mixture is refluxed for 1 hour, then is cooled to 25°C, is diluted with 80 ml of water and is filtered. The filtrate is stirred for 16 hours with 20 ml of aqueous formaldehyde and the product precipitates as a white solid, MP 118° to 123°C, net 5.6 grams, yield, 40% of the theoretical.

9-(3-Dimethylaminopropionyl)-2-Dimethylsulfamylthioxanthene: To a mixture of 9-acetyl-2-dimethylsulfamylthioxanthene (54.1 grams, 0.155 mol), 100 ml isopropanol, 10.6 grams paraformaldehyde and 16.4 grams (0.200 mol) dimethylamine hydrochloride, is added 1.0 milliliter of concentrated hydrochloric acid. The mixture is refluxed in a nitrogen atmosphere for 24 hours, then is concentrated to one-half volume by distillation of part of the solvent in vacuo. The concentrate is treated with 60 ml of ethyl acetate then the mixture is cooled to 5°C whereupon the crystalline product precipitates. This is removed by filtration and, after drying, weighs 47.8 grams, and melts at 177° to 181°C. After two crystallizations from isopropanol the product is obtained as the monohydrochloride addition salt, MP 187° to 189°C.

9-[3-(4-Methyl-1-Piperazinyl)-1-Hydroxypropyl]-2-Dimethylsulfamylthioxanthene: A mixture of 9-(3-dimethylaminopropionyl)-2-dimethylsulfamylthioxanthene hydrochloride (17 grams, 0.039 mol) and 20.0 grams (0.2 mol) 1-methylpiperazine in 40 ml of isopropanol is refluxed in a nitrogen atmosphere for 3 hours. 200 ml ethyl acetate is then added and the mixture is washed twice with 100 ml of water, the organic layer is separated and dried with anhydrous sodium sulfate, then the solvent is removed by distillation in vacuo. The 9-[3-(4-methyl-1-piperazinyl)propionyl]-2-dimethylsulfamylthioxanthene which remains as a residue is treated with a solution of 3.03 grams (0.08 mol) of sodium borohydride in 100 ml of ethanol. The mixture is refluxed under nitrogen for 3 hours, is cooled and is treated with an equal volume of water. The aminoalcohol is extracted 3 times with equal volumes of ethyl acetate. The organic layer is separated and is dried with anhydrous magnesium sulfate, then the solvent is removed by distillation leaving the product as a white, amorphous solid.

9-[3-(4-Methyl-1-Piperazinyl)-Propylidene]-2-Dimethylsulfamylthioxanthene: A solution of 12 grams of 9-[3-(4-methyl-1-piperazinyl)-1-hydroxypropyl]-2-dimethylsulfamylthioxanthene in 20 ml of pyridine is cooled to 0°C in an ice bath and 18.4 ml of phosphorus oxychloride dissolved in 60 ml of pyridine is added dropwise. The mixture is allowed to warm to 25°C during 30 minutes, then is heated, immersed in an 80°C oil bath, for an additional 30 minutes. The dark brown reaction mixture is cooled to 25°C then is poured onto 50 grams of ice. After the ice has melted, the aqueous solution is saturated with potassium carbonate and the liberated oil is extracted with three 150 ml portions of ethyl acetate. The solvents are removed from the separated organic layer by distillation. The product, a light brown amorphous solid, remains as a residue from the distillation. The free base is dissolved in 50 ml of acetone, is treated with two stoichiometric equivalents of maleic acid in 50 ml of acetone and the white crystalline dimaleate salt is removed by filtration. There is obtained 12.3 grams, 47% yield, MP 158° to 160.5°C (after recrystallization from ethanol).

References

Kleeman & Engel p. 894
PDR p. 1528
OCDS Vol. 1 p. 400 (1977) & 2, 412 (1980)
DOT 4 (4) 163 (1968) & 9 (6) 229 (1973)
I.N. p. 955
REM p. 1091
Bloom, B.M. and Muren, J.F.; U.S. Patent 3,310,553; March 21, 1967; assigned to Chas. Pfizer & Co., Inc.

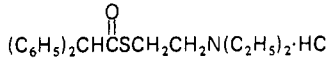
THIPHENAMIL HYDROCHLORIDE

Therapeutic Function: Antispasmodic

Chemical Name: α-phenylbenzeneethanethioic acid S-[2-(diethylamino)ethyl] ester hydrochloride

Common Name: 2-diethylaminoethyl diphenylthiolacetate hydrochloride

Structural Formula:



$$(C_6H_5)_2CHCSCH_2CH_2N(C_2H_5)_2 \cdot HCl$$

Chemical Abstracts Registry No.: 548-68-5; 82-99-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Trocinate	Poythress	U.S.	1950

Raw Materials

2-Diethylaminoethanethiol
Diphenylacetyl chloride

Manufacturing Process

The following procedure is described in U.S. Patent 2,510,773: To an ice-cold solution of 13.3 grams of 2-diethylaminoethanethiol in 100 cc of dry benzene is slowly added a solution of 23.05 grams of diphenylacetyl chloride in 200 cc of dry benzene. The mixture is stirred 2 hours, then heated to dissolve the fine white solid that is formed. Upon cooling 31.3 grams of 2-diethylaminoethyl diphenylthiolacetate hydrochloride precipitates. It recrystallizes from a mixture of benzene and petroleum ether (BP 60° to 70°C) as rosettes of tiny needles and melts at 129° to 130°C. From a mixture of absolute ethanol and ethyl acetate it recrystallizes as large, almost transparent prisms.

References

Merck Index 9215
REM p. 919
Richardson, A.G.; U.S. Patent 2,390,555; December 11, 1945; assigned to William P. Poythress & Company, Inc.
Clinton, R.O.; U.S. Patent 2,510,773; June 6, 1950; assigned to Sterling Drug Inc.

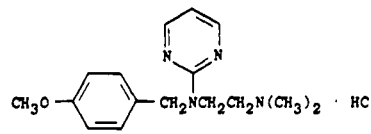
THONZYLAMINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: N-[(4-Methoxyphenyl)methyl]-N,N'-dimethyl-N-2-pyrimidinyl-1,2-ethanediamine monohydrochloride

Common Name: –

Structural Formula:



$$CH_3O-C_6H_4-CH_2NCH_2CH_2N(CH_3)_2-C_4H_3N_2 \cdot HCl$$

Chemical Abstracts Registry No.: 63-56-9

Trade Name	Manufacturer	Country	Year Introduced
Neohetramine	Warner Lambert	U.S.	1948
Anahist	Warner Lambert	U.S.	1949
Tonamil	Ecobi	Italy	–

Raw Materials

2-(p-Methoxybenzyl)aminopyrimidine
Sodium amide
Dimethylaminoethyl chloride

Manufacturing Process

54 g of 2-(p-methoxybenzyl)aminopyrimidine and 12.0 g of sodamide were suspended in 250 cc of toluene and were refluxed for 31 hours. To the thus prepared sodium salt of 2-(p-methoxybenzyl)aminopyrimidine, 28.1 g of dimethylaminoethyl chloride were added and refluxed under continuous stirring for 26 hours. After cooling, the reaction mixture was extracted with dilute hydrochloric acid at about pH 5.0, removing the product thus formed containing only very little of the unreacted 2-(p-methoxybenzyl)aminopyrimidine. This solution was then made alkaline to liberate the free base of the product, which was extracted with ether. The ether solution was evaporated and the residue vacuum distilled. The product, 2-(p-methoxybenzyl, dimethylaminoethyl)aminopyrimidine forms an oily liquid, boiling point 185°C to 187°C at 2.2 mm.

References

Merck Index 9219
OCDS Vol. 1 p. 52 (1977)
I.N. p. 947
Friedman, H.L. and Tolstoouhov, A.V.; U.S. Patent 2,465,865; March 29, 1949; assigned to Pyridium Corp.

TIADENOL

Therapeutic Function: Cholesterol-reducing agent

Chemical Name: 2,2'-(decamethylenedithio)diethanol

Common Name: –

Structural Formula: $HOCH_2CH_2S(CH_2)_{10}SCH_2CH_2OH$

Chemical Abstracts Registry No.: 6964-20-1

Trade Name	Manufacturer	Country	Year Introduced
Fonlipol	Lafon	France	1972
Tiaden	Malesci	Italy	1979
Braxan	Bago	Argentina	–
Delipid	Coop. Farm.	Italy	–
Eulip	Robin	Italy	–
Millaterol	Therapia	Spain	–
Tiaclar	C.I.	Italy	–
Tiodenol	Leti	Spain	–

Raw Materials

Thioethylene glycol
Decamethylene bromide

Manufacturing Process

Thioethylene glycol, $HSCH_2CH_2OH$ (prepared from ethylene oxide and hydrogen sulfide) is first reacted with sodium to give $HOCH_2CH_2SNa$. It is then reacted with decamethylene bromide, $Br(CH_2)_{10}Br$ to give tiadenol.

References

Merck Index 9263
Kleeman & Engel p. 881
DOT 8 (12) 454 (1972)
I.N. p. 948
Williams, J.L.R. and Cossar, B.C.; U.S. Patent 3,021,215; February 13, 1962; assigned to Eastman Kodak Company

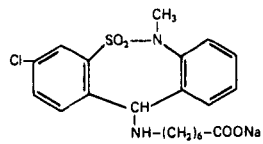
TIANEPTINE

Therapeutic Function: Antidepressant

Chemical Name: Sodium 7-[8-chloro-10-dioxo-11-methyldibenzo[c,f] thiazepin-(1,2)-5-yl]-aminoheptanoate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 66981-73-5

Trade Name	Manufacturer	Country	Year Introduced
Stablon	Servier	France	1983

Raw Materials

Ethyl 7-aminoheptanoate
5,8-Dichloro-10-dioxo-11-methyldibenzo[c,f] thiazepine(1,2)
Sodium hydroxide

Manufacturing Process

A solution of 27.6 g (0.16 mol) of freshly distilled ethyl 7-aminoheptanoate in 40 ml of nitromethane was added all at once and with mechanical stirring to a suspension of 26.2 g (0.08 mol) of 5,8-dichloro-10-dioxo-11-methyldibenzo[c,f] thiazepine(1,2) in 120 ml of nitromethane. The whole was heated to 55°C for 30 minutes, the solvent was then evaporated in vacuo and the residue was taken up in water. The crude ester was extracted with ether. After evaporation of the ether 36 g of crude ester were obtained, and 30 g (0.065 mol) thereof were treated under reflux with a solution of 2.8 g (0.07 mol) of sodium hydroxide in 75 ml of eth-

anol and 25 ml of water. After one hour's refluxing, the alcohol was evaporated in vacuo. The residue was taken up in 150 ml of water.

The mixture was twice extracted with 75 ml of chloroform and the aqueous phase was evaporated in vacuo. The sodium salt was then dissolved in 150 ml of chloroform, the solution was dried over sodium sulfate and the product precipitated with anhydrous ether.

The salt was filtered off, washed with ether and dried at 50°C. 13 g of sodium 7-[8-chloro-10-dioxo-11-methyldibenzo[c,f] thiazepin-(1,2)-aminoheptanoate, melting with decomposition at about 180°C, were obtained.

References

Merck Index 9265
DFU 4 (7) 522 (1979) (As S-1574) & 6 (12) 797 (1981)
DOT 19 (6) 306 (1983)
Malen, C., Danree, B. and Poignant, J.C.; U.S. Patents 3,758,528; September 11, 1973; and 3,821,249; June 28, 1974; both assigned to Societe et Nom Collectif Science Union et Cie, Societe Francaise de Recherche Medicale

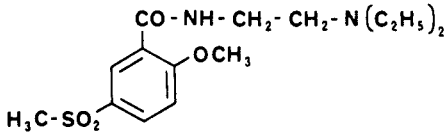
TIAPRIDE

Therapeutic Function: Antiemetic

Chemical Name: N-(Diethylaminoethyl)-2-methoxy-5-methylsulfonylbenzamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 51012-32-9; 51012-33-0 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Tiapridal	Delagrange	France	1977
Tiapridex	Schuerholz	W. Germany	1977
Sereprile	Vita	Italy	1977
Tiapridal	Pharmos	Switz.	1981
Italprid	Prophin	Italy	–
Neuropri	Italchemi	Italy	–

Raw Materials

2-Methoxy-5-methylsulfonylbenzoic acid
Isobutyl chloroformate
N,N-diethylethylenediamine

Manufacturing Process

5 g of 2-methoxy-5-methylsulfonylbenzoic acid, 50 ml of dioxan, 3.02 ml of triethylamine and 3 g of isobutyl chloroformate were introduced into a 250 ml balloon flask at ambient temperature.

After the mixture had been stirred for 30 minutes, 3 g of N,N-diethylethylenediamine were added. The reaction mixture was stirred for 6 hours and the solvents were evaporated under vacuum.

The residue was dissolved in 50 ml of water and the solution was made alkaline with sodium hydroxide. The precipitate formed was filtered, washed and dried in a drying oven at 60°C. 6 g of N-(diethylaminoethyl)-2-methoxy-5-methylsulfonylbenzamide (melting point: 124°C to 125°C) was produced.

References

DFU 1 (2) 88 (1976)
Kleeman & Engel p. 881
DOT 13 (8) 340 (1977)
I.N. p. 949
Societe d'Etudes Scientifiques et Industrielles de l'Ile-de-France; British Patent 1,394,563; May 21, 1975

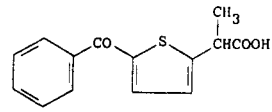
TIAPROFENIC ACID

Therapeutic Function: Antiinflammatory

Chemical Name: 5-Benzoyl-α-methyl-2-thiopheneacetic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 33005-95-7

Trade Name	Manufacturer	Country	Year Introduced
Surgam	Roussel	France	1975
Surgam	Roussel	W. Germany	1980
Surgam	Hoechst	Switz.	1982
Surgam	Roussel	U.K.	1982
Surgamic	Roussel-Iberica	Spain	–

Raw Materials

Thiophene-2α-methylacetic acid
Benzoyl chloride

Manufacturing Process

A mixture of 10.3 g of thiophene-2α-methylacetic acid [prepared by process of Bercot-Vatteroni, et al., *Bull. Soc. Chim.* (1961) pp. 1820-21], 11.10 g of benzoyl chloride and a suspension of 23.73 g of aluminum chloride in 110 cc of chloroform was allowed to stand for 15 minutes and was then poured into a mixture of ice and hydrochloric acid. The chloroform phase was extracted with a 10% aqueous potassium carbonate solution and the aqueous alkaline phase was acidified with N hydrochloric acid and was then extracted with ether. The ether was evaporated off and the residue was crystallized from carbon tetrachloride to obtain a 54% yield of 5-benzoyl-thiophene-2α-methylacetic acid melting at 83°C to 85°C. The

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)

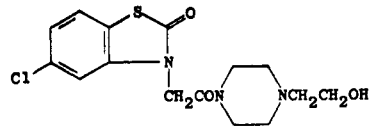
TIARAMIDE

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