S

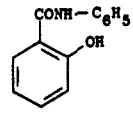
SALICYLANILIDE

Therapeutic Function: Antifungal

Chemical Name: 2-hydroxy-N-phenylbenzamide

Common Name: N-phenylsalicylamide

Structural Formula:



Chemical Abstracts Registry No.: 87-17-2

Trade Name	Manufacturer	Country	Year Introduced
Salinidol	Doak	U.S.	1946
Ansadol	Rorer	U.S.	1947
Hyanilid	Peau Seche	U.S.	–

Raw Materials

Salicylic acid
Aniline

Manufacturing Process

Salicylanilide is ordinarily made by reacting salicylic acid with aniline in the presence of phosphorus trichloride at an elevated temperature. The theoretical proportions of reactants are usually employed for best results, that is, one mol each of aniline and salicylic acid to a third of a mol of phosphorus trichloride. An improved process employs an inert organic solvent as a reaction diluent.

References

Merck Index 8188
I.N. p. 861
Majewski, T.E., Parsey, E.S. and Skelly, N.E.; U.S. Patent 3,221,051; November 30, 1965
Majewski, T.E., Stoesser, W.C. and Parsey, E.S.; U.S. Patent 3,231,611; January 25, 1966; assigned to The Dow Chemical Company

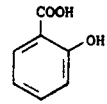
SALICYLIC ACID

Therapeutic Function: Keratolytic

Chemical Name: 2-Hydroxybenzoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 69-72-7

Trade Name	Manufacturer	Country	Year Introduced
Saligel	Stiefel	U.S.	1978
Fomac	Dermik	U.S.	1979
Aveenobar	Rydelle	U.S.	–
Barseb	Barnes-Hind	U.S.	–
Cantharone	Seres	U.S.	–
Compound W	Whitehall	U.S.	–
Duofilm	Stiefel	U.S.	–
Egocappol	Ego	Australia	–
Fostex	Westwood	U.S.	–
Fungi-Nail	Kramer	U.S.	–
Hydrisalic	Pedinol	U.S.	–
Jabon Salicilico	Imba	Spain	–
Keralyt	Westwood	U.S.	–
Komed	Barnes-Hind	U.S.	–
Night-Cast	Seres	U.S.	–
Occlusal	Gen Derm	U.S.	–
Pernox	Westwood	U.S.	–
Sal Ac	Gen Derm	U.S.	–
Salactic	Pedinol	U.S.	–
Sebucare	Westwood	U.S.	–
Sebulex	Westwood	U.S.	–
Tinver	Barnes-Hind	U.S.	–
Verrex	C & M	U.S.	–
Verrusal	C & M	U.S.	–
Viranol	Amer. Dermal	U.S.	–
Wart-Off	Pfipharmecs	U.S.	–
Whitfield's Ointment	Fougera	U.S.	–

Raw Materials

Sodium phenolate
Bacterium *Pseudomonas*
Nutrient medium
Carbon dioxide
Naphthalene

Manufacturing Process

Made by reacting sodium phenolate and carbon dioxide. May also be made by microbiological oxidation of naphthalene by forming an aqueous nutrient medium for microorganisms capable of oxidizing naphthalene to salicylic acid of the genus *Pseudomonas* containing basal mineral salts, 0.5 to 4 wt % of finely divided naphthalene and 0.1 to 1 wt % of a boron compound, inoculating the nutrient medium with an inoculum containing a microorganism capable of oxidizing naphthalene to salicylic acid of the genus *Pseudomonas,* the inoculated nutrient medium having an initial pH value of about 4 to 9, incubating the inoculated nutrient medium at a temperature of about 25° to 50°C for a period of about 2 to 7 days and then recovering salicylic acid from the nutrient medium.

References

Merck Index 8190
PDR pp. 580, 653, 777, 905, 985, 1397, 1417, 1575, 1696, 1779, 1890, 1898
I.N. p. 37
REM p. 785
Zajic, J.E. and Dunlap, W.J.; U.S. Patent 3,274,074; September 20, 1966; assigned to Kerr-McGee Oil Industries, Inc.

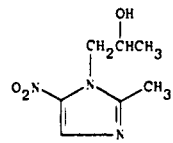
SECNIDAZOLE

Therapeutic Function: Antiamebic; antiprotozoal

Chemical Name: α,2-Dimethyl-5-nitro-1H-imidazole-1-ethanol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 3366-95-8

Trade Name	Manufacturer	Country	Year Introduced
Flagentyl	Rhone Poulenc	Switz.	1980

Raw Materials

1-(2-Acetoxypropyl)-2-methylimidazole
Nitric acid
Hydrogen chloride

Manufacturing Process

1-(2-Acetoxypropyl)-2-methylimidazole (18.2 g) is gradually dissolved in fuming nitric acid (d = 1.52; 25 cc) with stirring, the temperature being kept at about 2°C. Phosphorus pentoxide (20 g) is added, with caution, to the resulting solution and while maintaining the temperature at about 2°C. Afterwards, the reaction mixture is stirred for a further 3 hours 30 minutes at 2°C and poured onto ice (180 g).

The solution obtained is treated with ammonium hydroxide (d = 0.92; 105 cc), saturated with sodium chloride, and then extracted with ethyl acetate (total 650 cc). The combined organic extracts are washed with a saturated aqueous sodium chloride solution (50 cc) and then dried over sodium sulfate. The volatile products are evaporated under reduced pressure (20 mm Hg) and a mixture of 1-(2-acetoxypropyl)-2-methyl-4-nitroimidazole and 1-(2-acetoxypropyl)-2-methyl-5-nitroimidazole (18.6 g) is obtained in the form of a red oil.

A solution of a mixture of 1-(2-acetoxypropyl)-2-methyl-4-nitroimidazole and of 1-(2-acetoxypropyl)-2-methyl-5-nitroimidazole (18.6 g) (prepared as described above) in 4N hydrochloric acid (186 cc) is heated at 90°C for 90 minutes. The cooled solution is treated with ammonium hydroxide (d = 0.9; 100 cc), saturated with sodium chloride, and then extracted with ethyl acetate (total 550 cc). The combined organic extracts are washed with a saturated aqueous

sodium chloride solution (50 cc) and then dried over sodium sulfate. The volatile products are evaporated under reduced pressure (25 mm Hg); the residual brown oil weighs 9.2 g.

This oil (5.8 g) is dissolved in methyl ethyl ketone (20 cc) and chromatographed over silica (232 g) contained in a column 4.5 cm in diameter. The column is eluted with methyl ethyl ketone; the first 600 cc of eluate are discarded and 500 cc of eluate are then collected and concentrated under reduced pressure (25 mm Hg); a partially crystalline product (2.4 g) is thus obtained. 1-(2-Hydroxypropyl)-2-methyl-5-nitroimidazole (0.96 g), melting point 72°C, is obtained on recrystallization from water (4 cc).

References

Merck Index 8267
DFU 4 (4) 280 (1979)
Kleeman & Engel p. 817
DOT 17 (2) 62 (1981)
I.N. p. 867
Jeanmart, C. and Messer, M.N.; British Patent 1,278,757; June 21, 1972; assigned to Rhone-Poulenc S.A. (France)

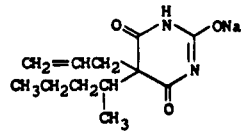
SECOBARBITAL SODIUM

Therapeutic Function: Hypnotic

Chemical Name: 5-(1-methylbutyl)-5-(2-propenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione monosodium salt

Common Name: Meballymal sodium; quinalbarbitone sodium

Structural Formula:



Chemical Abstracts Registry No.: 309-43-3; 76-73-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Seconal	Lilly	U.S.	1945
Dormatylan	Herz-Jesu-Apotheke	Austria	–
Dormona	Wiedenmann	Switz.	–
Immenoctal	I.S.H.	France	–
Ional Sodium	Yoshitomi	Japan	–
Novosecobarb	Novopharm	Canada	–
Proquinal	Protea	Australia	–
Quinbar	Adams	Australia	–
Sebar	Vangard	U.S.	–
Secaps	Saunders	Canada	–
Secocaps	M.T.C.	Canada	–
Secogen	Paul Maney	Canada	–
Seral	Medic	Canada	–
Tuinal	Lilly	U.S.	–

Raw Materials

Propyl-methyl-carbinyl barbituric acid
Allyl bromide
Sodium hydroxide

Manufacturing Process

Propyl-methyl-carbinyl allyl barbituric acid (also called allyl 1-methyl-butyl barbituric acid) may be prepared as follows: 1 mol of propyl-methyl-carbinyl barbituric acid is dissolved in a suitable vessel in a 10 to 35% aqueous solution of 1 mol of potassium hydroxide. To this are added somewhat in excess of 1 mol of allyl bromide, and alcohol equal to about 10% of the total volume of the solution. The vessel is agitated for 50 to 75 hours. At the end of this time, the solution, which may still exhibit two layers, is concentrated to about one-half its volume to remove the excess allyl bromide and the alcohol. On cooling, an oily layer, which is propyl-methyl-carbinyl allyl barbituric acid, separates out as a sticky viscous mass. It is dried, washed with petroleum ether, and dissolved in the minimum amount of benzene. Any unreacted propyl-methyl-carbinyl barbituric acid, which does not dissolve, is filtered off. The addition of petroleum ether to the clear filtrate causes the propyl-methyl-carbinyl allyl barbituric acid to precipitate as an oily mass.

This is separated, washed with petroleum ether, and dried in vacuo. After some time it hardens into a whitish solid, which if it was prepared from a 1-bromo-pentane which had some of its isomer 3-bromo-pentane copresent with it has a melting point of about 80° to 83°C. However, by using a pure 2-bromo-pentane, and/or by recrystallizing a number of times from dilute alcohol, the melting point may be raised to 98° to 100°C, corrected.

One part by weight of propyl-methyl-carbinyl allyl barbituric acid is added to enough alcohol to facilitate handling, in this case conveniently about six times its weight. To this is added a solution of sodium hydroxide, preferably carbonate-free or substantially so, containing $^{40}/_{238}$ parts by weight of sodium hydroxide, which is the amount of sodium hydroxide necessary to combine in equal molecular proportions with the propyl-methyl-carbinyl allyl barbituric acid. This solution is filtered clear, and is then evaporated under vacuum until the sodium propyl-methyl-carbinyl allyl barbiturate (alternatively named sodium allyl 1-methyl-butyl barbiturate) separates out in solid form. The salt as thus obtained in solid form contains a varying amount of moisture.

If it is desired to have a stable salt substantially free from contaminants, the alcohol used for dissolving the barbituric acid is absolute alcohol, and the sodium hydroxide is added as a very concentrated aqueous solution so that the reaction which occurs to form the salt is in a substantially alcoholic solution. By having a substantially alcoholic solution, decomposition of the salt during the process of drying is effectively avoided; and the drying may be carried to a point where materially less than 1% of moisture remains, so that the salt is substantially anhydrous. In this way a stable salt substantially free from decomposition products formed during preparation or drying or on standing is obtained. This salt may be used safely for making aqueous solutions for intravenous injection; for such aqueous solutions, when freshly made, are clear solutions substantially free from haziness.

Sodium propyl-methyl-carbinyl allyl barbiturate is a white hygroscopic solid, readily soluble in water and alcohol, and insoluble in ether.

References

Merck Index 8268
Kleeman & Engel p. 816
PDR pp. 1067, 1989
OCDS Vol. 1 p. 269 (1977)
I.N. p. 867
REM p. 1068
Shonle, H.A.; U.S. Patent 1,954,429; April 10, 1934; assigned to Eli Lilly and Company

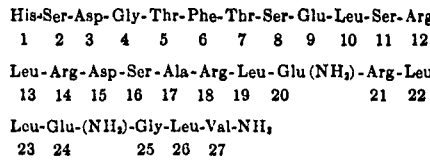
SECRETIN

Therapeutic Function: Diagnostic aid (organ function)

Chemical Name: A complex polypeptide

Common Name: –

Structural Formula:



It is a peptide containing 27 amino acid residues containing the amino acids: L-histidine (His); L-aspartic acid (Asp); L-serine (Ser); glycine (Gly); L-threonine (Thr); L-phenylalanine (Phe); L-glutamic acid (Glu); L-glutamine [Glu(NH_2)]; L-leucine (Leu); L-arginine (Arg); L-alanine (Ala); and L-valinamide (Val-NH_2).

The above mentioned peptide salts include, for instance, hydrochlorides, hydrobromides, acetates, fluoroacetates, such as trifluoroacetate, and chloroacetates such as dichloroacetate.

Chemical Abstracts Registry No.: 1393-25-5

Trade Name	Manufacturer	Country	Year Introduced
Secretin-Boots	Warren-Teed	U.S.	1970
Secretin-Kabi	Kabi	U.S.	1981
Secrepan	Eisai	Japan	–
Secretine Sinbio	Fimex	France	–
Secretolin	Hoechst	–	–

Raw Materials

Tetrapeptide: L-Thr-L-Phe-L-Thr-L-Ser
Tetrapeptide: L-His-L-Ser-β-Benzyl-L-Asp-L-Gly

Manufacturing Process

The gastrointestinal hormone secretin is prepared by fragment condensation. The tetrapeptide L-Thr-L-Phe-L-Thr-L-Ser is coupled to the C-terminal nonadecapeptide of the hormone, and the tetrapeptide L-His-L-Ser-β-benzyl-L-Asp-Gly is coupled to the tricosapeptide resulting from the first coupling.

References

Merck Index 8269
Kleeman & Engel p. 817
PDR p. 1428
DOT 10 (6) 210 (1974) & 16 (3) 87 (1980)
I.N. p. 868
REM p. 1277

Bodanszky, M., Ondetti, M.A., von Saltza, M.H., Narayanan, V.L. and Levine, S.D.; U.S. Patent 3,767,639; October 23, 1973; assigned to E.R. Squibb & Sons, Inc.

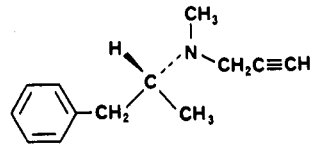
SELEGILINE

Therapeutic Function: Antidepressant

Chemical Name: N-(1-Phenylisopropyl)-N-methyl-prop-2-ynylamine

Common Name: Deprenil, deprenaline

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Eldepryl	Britannia	U.K.	1982
Deprenyl	Egyt	Hungary	–
Jumex	Medimpex	Hungary	–

Raw Materials

L-N-(2-phenylisopropyl)methylamine
Propargyl bromide

Manufacturing Process

50 g of L-N-(2-phenylisopropyl)methylamine are dissolved in 62.5 ml of toluene, whereupon 13 ml of propargyl bromide are added dropwise within about 20 minutes at a temperature in the range of 50°C to 60°C. The reaction mixture is stirred at 80°C for 3 hours, whereupon it is cooled and the toluene solution is extracted with 125 ml of a 5% hydrochloric acid solution. The acidic layer is separated and made alkaline. The precipitated oil is isolated, washed with benzene and evaporated. The residue is subjected to fractional distillation in vacuo. L-N-(2-phenylisopropyl)methylamine distills off at 65°C to 67°C (0.6 mm Hg, n_D^{20} = 1.5083). The L-N-(1-phenylisopropyl)-N-methyl-prop-2-ynylamine is obtained at 92°C to 93°C (0.8 mm Hg, n_D^{20} = 1.5180). The melting point of the hydrochloride is 141°C.

References

Merck Index 2876
DFU 4 (2) 128 (1979)
DOT 19 (1) 29 (1983)
I.N. p. 869
Chinoin Gyogyszer- es Vegyeszeti Termekek Gyara R.T.; British Patents 1,031,425; June 2, 1966; and 1,153,578; May 29, 1969

SELENIUM SULFIDE

Therapeutic Function: Dermatological

Chemical Name: Selenium sulfides

Common Name: –

Structural Formula: Se_4S_4 and Se_2S_6

Chemical Abstracts Registry No.: 7488-56-4

Trade Name	Manufacturer	Country	Year Introduced
Selsun	Abbott	U.S.	1951
Bioselenium	Uriach	Spain	–
Caspiselenio	Kin	Spain	–
Exsel	Herbert	U.S.	–
Iosel	Owen	U.S.	–
Sebusan	Laake	Finland	–
Selenol	N. D. & K.	Denmark	–
Sel-O-Rinse	U.S.V.	U.S.	–
Selsorin	Farmos	Finland	–
Selsun Blue	Ross	U.S.	–
Selukos	Kabi	W. Germany	–

Raw Materials

Selenious acid
Hydrogen sulfide

Manufacturing Process

Selenium disulfide, SeS_2, may be made by the reaction of selenious acid, H_2SeO_3, and hydrogen sulfide. Its manufacture is described by B.W. Nordlander in U.S. Patents 1,860,154 and 1,860,336. It is prepared in a detergent suspension for therapeutic use.

References

Merck Index 8283
PDR pp. 552, 930, 1563
I.N. p. 869
REM p. 1165
Baldwin, M.M. and Young, A.P. Jr.; U.S. Patent 2,694,669; November 16, 1954; assigned to Abbott Laboratories

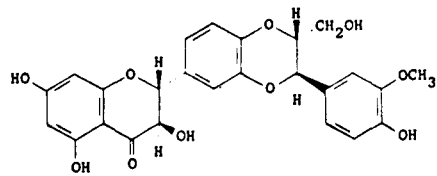
SILYMARIN

Therapeutic Function: In liver dysfunction

Chemical Name: 2-[2,3-Dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl] -2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one

Common Name: Silybin, silibinine

Structural Formula:



Chemical Abstracts Registry No.: 27359-03-1

Trade Name	Manufacturer	Country	Year Introduced
Legalon	Madaus	W. Germany	1969
Legalon	I.B.I.	Italy	1971
Legalon	Roger Bellon	France	1974
Silliver	Abbott	Italy	1977
Apihepar	Panchemie Homburg	Austria	—
Cardomerin	Deiters	Spain	—
Cronol	Kappa	Spain	—
Dura Silymarin	Durachemie	W. Germany	—
Emil	Horus	Spain	—
Eparfit	Europa	Spain	—
Escarmine	Dreikehl	Spain	—
Flavobion	Spofa	Czechoslovakia	—
Halodren	Escaned	Spain	—
Hepadestal	Krugmann	W. Germany	—
Hepagerina	Kairon	Spain	—
Hepalar	Larma	Spain	—
Hepallolina	Calloi	Spain	—
Hepato-Framan	Oftalmiso	Spain	—
Laragon	Roemmers	Argentina	—
Sematron	Madariaga	Spain	—
Silarine	Vir	Spain	—
Silepar	Ibirn	Italy	—
Silgen	Morgens	Spain	—
Silibancol	Durban	Spain	—
Silimazu	Mazuelos	Spain	—
Silirex	Lampugnani	Italy	—

Raw Materials

Silybum marianum fruit
Ethyl acetate

Manufacturing Process

Silymarin comprising polyhydroxyphenyl chromanones is recovered from the dried fruit of *Silybum marianum* Gaertn. by separating the fatty oils therefrom, extracting the remaining solid residue with ethyl acetate, evaporating the ethyl acetate and dissolving the dry residue in a solvent mixture comprising methanol, water and petroleum ether to form a two-phase system wherein the chromanones are contained in the lower phase, recovering the polyhydroxyphenyl chromanones from the lower phase after subjecting same to multiple countercurrent contact with petroleum ether.

References

Merck Index 8372
Kleeman & Engel p. 818
DOT 7 (6) 216 (1971)
I.N. p. 873
Madaus, R.; U.S. Patent 3,773,932; November 20, 1973; assigned to Dr. Madaus & Co. (Germany)

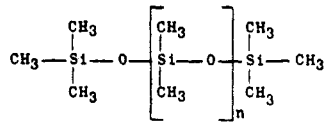
SIMETHICONE

Therapeutic Function: Antiflatulent

Chemical Name: Dimethyl polysiloxane

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 8050-81-5

Trade Name	Manufacturer	Country	Year Introduced
Mylicon	Stuart	U.S.	1960
Silain	Robins	U.S.	1961
Celluzyme	Dalin	U.S.	–
Gelusil	Parke Davis	U.S.	–
Mylanta	Stuart	U.S.	–
Phazyme	Reed & Carnrick	U.S.	–
Riopan-Plus	Ayerst	U.S.	–
Simeco	Wyeth	U.S.	–
Tri-Cone	Glaxo	U.S.	–

Raw Materials

Dimethyl diethoxy silane
Trimethyl ethoxy silane
Sodium hydroxide

Manufacturing Process

In a 5 liter three-necked flask, fitted with a reflux condenser, agitator and thermometer, were placed 1,393 grams (9.41 mols) of redistilled $(CH_3)_2Si(OEt)_2$ and 1,110 grams (9.41 mols) of $(CH_3)_3SiOEt$. To this solution was added 254 grams (14.11 mols) of water containing 7.5 grams of NaOH, (approximately 1 NaOH per 100 silicon atoms). This insured the formation of only straight chain polymers. The mixture was heated to 40°C and the temperature continued to rise for nearly an hour. After adding 50 cc (20% excess) more water, the mixture was refluxed for two hours and then allowed to stand overnight.

Alcohol was then distilled off, until the temperature reached 100°C. 1,706.6 grams of distillate was collected (theory 1,430 grams). This alcohol was poured into four times its volume of water and an insoluble oil separated (457 grams). The insoluble fraction was added back to the copolymer residue from the distillation and 555 cc of 20% hydrochloric acid was added. The acid mixture was refluxed for two hours, and the silicon oils were carefully washed with distilled water until neutral. The yield was 1,420 grams (theory, 1,469 grams).

References

Merck Index 8374
PDR pp. 650, 829, 916, 1352, 1444, 1569, 1783, 1981
REM p. 814
Hyde, J.F.; U.S. Patent 2,441,098; May 4, 1948; assigned to Corning Glass Works

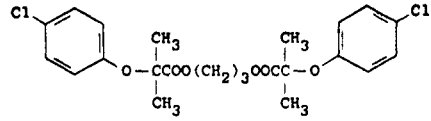
SIMFIBRATE

Therapeutic Function: Cholesterol-reducing agent

Chemical Name: 2-(4-chlorophenoxy)-2-methylpropanoic acid 1,3-propanediyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 14929-11-4

Trade Name	Manufacturer	Country	Year Introduced
Cholesorbin	Takeda	Japan	1971
Cholesolvin	Cyanamid	Italy	1977
Liposolvin	Tosi-Novara	Italy	–

Raw Materials

α-(p-Chlorophenoxy)isobutyric acid
1,3-Propanediol

Manufacturing Process

A mixture of 22 grams of α-(p-chlorophenoxy)isobutyric acid, 3.8 grams of 1,3-propanediol, 0.5 gram of p-toluenesulfonic acid and 150 ml of xylene was refluxed. When the theoretically calculated amount of water had been removed, the xylene solution was washed with dilute aqueous sodium bicarbonate and then the xylene was distilled off. The residue was distilled under reduced pressure to give 11 grams (47% yield) of 1,3-propanediol bis[α-(p-chlorophenoxy)isobutyrate] boiling at 197° to 200°C/0.03 mm Hg.

References

Merck Index 8377
Kleeman & Engel p. 819
DOT 7 (6) 221 (1971)
I.N. p. 874
Nakanishi, M., Kuriyama, T., Oe, T. and Kobayakawa, T.; U.S. Patent 3,494,957; Feb. 10, 1970; assigned to Yoshitomi Pharmaceutical Industries, Ltd., Japan

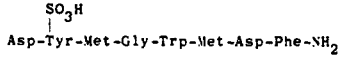
SINCALIDE

Therapeutic Function: Choleretic

Chemical Name: 1-De(5-oxo-L-proline)-2-de-L-glutamine-5L-methioninecaerulein

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 25126-32-3

Trade Name	Manufacturer	Country	Year Introduced
Kinevac	Squibb	U.S.	1976
Kinevac	Squibb	W. Germany	1977

Raw Materials

t-Butyloxycarbonyl-L-aspartyl-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide
Sulfuric Acid

Manufacturing Process

The starting material in the following synthesis is: t-butyloxycarbonyl-L-aspartyl-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide designated (SM).

(A) A solution of (SM) (320 mg) in trifluoroacetic acid (7 ml) was kept under nitrogen at room temperature for 15 minutes. Ether (100 ml) was added and the precipitate filtered, washed thoroughly with ether and dried. This material (280 mg) was added to concentrated sulfuric acid (20 ml), cooled at -20°C. The solution was kept in the dry ice-acetone bath at -20°C for 75 minutes. The sulfuric acid solution was poured into ice water (80 ml). The precipitate was centrifuged, resuspended in ice water (30 ml) and 4N sodium hydroxide was added until a clear solution was obtained. After reacidification to pH 4 with dilute sulfuric acid, the precipitate formed was centrifuged, washed twice with ice water and dried. Yield 155 mg. Chromatograph of DEAE Sephadex (with ammonium carbonate buffer) yielded the desired octapeptide sulfate ester: 30 mg.

(B) A solution of (SM) (330 mg) in trifluoroacetic acid (7 ml) was kept under nitrogen at room temperature for 15 minutes. Ether (100 ml) was added and the precipitate was filtered, washed thoroughly with ether and dried. This material (300 mg) was added in portions to concentrated sulfuric acid (18 ml) cooled at -20°C with vigorous stirring. After 15 minutes a solution of potassium bisulfate in concentrated sulfuric acid (408 mg in 3 ml) was added. The reaction mixture was stirred for 75 minutes at -15°C and then stored at -7°C for 285 minutes. The sulfuric acid solution was poured into cold ether (400 ml); precipitate was filtered, washed with cold ether, and suspended in cold water. Complete solution was then achieved by careful addition of 2N sodium hydroxide. Acidification with N hydrochloric acid led to the precipitation of the desired octapeptide sulfate ester. Yield 200 mg.

References

Merck Index 8380
DOT 13 (9) 356 (1977)
I.N. p. 874
REM p. 1277
Ondetti, M.A., Pluscec, J., Sheehan, J.T., Jorpes, J.E. and Mott, V.; U.S. Patent 3,723,406; March 27, 1973; assigned to E.R. Squibb & Sons, Inc.

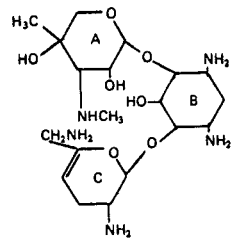
SISOMICIN

Therapeutic Function: Antibiotic

Chemical Name: O-2,6-diamino-2,3,4,6-tetradeoxy-α-D-glycero-hex-4-enopyranosyl-(1→4)-O-[3-deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)]-2-deoxy-D-streptamine

Common Name: Rickamicin

Structural Formula:



Chemical Abstracts Registry No.: 32385-11-8; 53179-09-2 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Pathomycin	Byk-Essex	W. Germany	1976
Extramycin	Bayer	W. Germany	1976
Extramycin	Bayer	Switz.	1978
Baymicina	Bayer	Italy	1978
Sisomin	Schering	Switz.	1978
Sisomicin	Essex	Italy	1978
Mensiso	Menarini	Italy	1979
Sissolline	Cetrane	France	1980
Siseptin	Essex	Japan	1981
Baymicine	Bayer	France	1981
Extramycin	Yoshitomi	Japan	1981

Raw Materials

Bacterium *Micromonspora inyoensis*
Dextrin
Soybean meal

Manufacturing Process

Tank fermentation of Micromonospora inyoensis — Germination stage 1: Under aseptic conditions, add a lyophilized culture (or cells obtained from a slant culture) of *M. inyoensis* to a 300 ml shake flask containing 100 ml of the following sterile medium:

Beef extract	3 g
Tryptone	5 g
Yeast extract	5 g
Dextrose	1 g
Starch	24 g
Calcium carbonate	2 g
Tap water	1,000 ml

Incubate the flask and its contents for 5 days at 35°C on a rotary shaker (280 rpm, 2" stroke).

Germination stage 2: Aseptically transfer 25 ml of the fermentation medium of Germination stage 1 to a 2-ℓ shake flask containing 500 ml of the abovedescribed sterile germination medium. Incubate the flask and its contents for 3 days at 28°C on a rotary shaker (280 rpm, 2" stroke).

Fermentation stage: Aseptically transfer 500 ml of the medium obtained from Germination stage 2 to a 14-ℓ fermentation tank containing 9.5 ℓ of the following sterile medium:

Dextrin	50 g
Dextrose	5 g
Soybean meal	35 g

Calcium carbonate	7 g
Cobalt chloride	10^{-6} M
Tap water	1,000 ml
Antifoam (GE 60)	10 ml

Prior to sterilizing the abovedescribed medium, adjust the pH to 8. Aerobically ferment for 66 to 90 hours while stirring at 250 rpm with air input at 4.5 ℓ/ℓ/min and 25 psi. The potency of the antibiotic produced at the end of this period reaches a peak of 150 to 225 μg/ml and remains relatively constant. The pH of the fermentation medium changes slightly during the antibiotic production, varying in the range of 6.8 to 7.3.

Isolation of Antibiotic 66-40 — The whole broth is adjusted to pH 2 with 6N sulfuric acid. (For the purpose of this example, quantities are given in terms of 170 ℓ of fermentation broth obtained by pooling acidified broth from 17 batches.) The acidified broth is stirred for about 15 minutes and then filtered. Wash the mycelium with water and combine the washings with the filtrate. Adjust the pH of the filtrate to 7 with 6N ammonium hydroxide.

To the neutralized filtrate, add sufficient oxalic acid to precipitate calcium and filter. Reneutralize the filtrate with ammonium hydroxide. Charge the filtrate onto a cationic exchange adsorption column containing 1,500 to 2,000 g of IRC-50 Amberlite in its ammonium form. Discard the eluate, wash the resin with water, and elute with 2N ammonium hydroxide. Collect 400 ml fractions and monitor by disc testing with *S. aureus* ATCC-6538P. Combine active fractions and evaporate to dryness under vacuum obtaining about 28 g of crude Antibiotic 66-40 having an activity of about 500 μg/g.

Purification of Antibiotic 66-40 — Dissolve 28 g of crude Antibiotic 66-40 in 100 ml of distilled water and charge to an anion exchange adsorption column (Dowex 1X2) in the hydroxyl form. Slurry 2,000 g of the resin in water into a column 2½" in diameter and 36" high. Elute the column with distilled water at a rate of about 23 ml/min collecting 100 ml fractions and monitor with a conductivity meter and by disc testing against *Staphylococcus aureus.*

The disc testing provides a gross separation of antibiotic-containing eluate fractions from those devoid of antibiotic. To insure that the fractions are properly combined, a portion of each fraction is paper chromatographed using the lower phase of a chloroform:methanol:17% ammonium hydroxide system (2:1:1). Each paper is sprayed with ninhydrin and the eluates containing like material are combined and lyophilized yielding about 5.7 g of Antibiotic 66-40 assaying about 900 μg/mg.

References

Merck Index 8384
Kleeman & Engel p. 819
DOT 8 (8) 315 (1972) & 12 (10) 407 (1976)
I.N. p. 875
REM p. 1183
Weinstein, M.J., Luedemann, G.M. and Wagman, G.H.; U.S. Patent 3,832,286; August 27, 1974; assigned to Schering Corp.

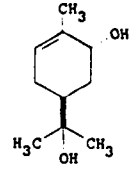
SOBREROL

Therapeutic Function: Mucolytic

Chemical Name: 5-Hydroxy-α,α,4-trimethyl-3-cyclohexene-1-methanol

Common Name: Pinol hydrate

Structural Formula:



Chemical Abstracts Registry No.: 498-71-5

Trade Name	Manufacturer	Country	Year Introduced
Sobrepin	Corvi	Italy	1970
Lysmucol	Schering	Switz.	1983

Raw Materials

α-Pinene oxide

Manufacturing Process

To 19 ℓ of well-agitated distilled water plus 18 g of ditertiary-butyl-p-cresol was added 19.84 kg (130 mols) of pure α-pinene oxide that was about half racemic, half d-form. The temperature was maintained at 30°C to 50°C, first with ice bath cooling and then with tap water cooling. The addition of the pinene oxide required 1½ hours. After the addition was complete and the exothermic reaction was about over, the mixture was stirred for 2½ hours at about 30°C, and then centrifuged to separate the crude sobrerol from the liquid phase consisting of oil and water.

The crude sobrerol was washed with naphtha and then air dried to yield 14.81 kg (87.5 mols) of pure sobrerol, $[\alpha]_D^{25} -77.0°$. It was found that 1 liter of the aqueous phase from the reaction contained 22 g of sobrerol, so, therefore, the entire aqueous phase contained 0.42 kg (2.5 mols) of sobrerol.

References

Merck Index 8395
I.N. p. 877
Klein, E.A.; U.S. Patent 2,815,378; December 3, 1957; assigned to The Glidden Co.

SOMATOTROPIN

Therapeutic Function: Growth stimulant

Chemical Name: See under Structural Formula

Common Name: Somatropin

Structural Formula: Proteins of molecular weights ranging from 22,124 for human growth hormone (HGH) to 47,400 for bovine growth hormone.

Chemical Abstracts Registry No.: 9002-72-6

Trade Name	Manufacturer	Country	Year Introduced
Somatotrope	Choay	France	1951
Wachtungshormon	Kabi	W. Germany	1970

Trade Name	Manufacturer	Country	Year Introduced
Crescormon	Sumitomo	U.K.	1973
Grorm	Serono	Italy	1975
Asellacrin	Calbiochem	U.S.	1976
Crescormon	Kabi	U.S.	1978
Nanormon	Hormon-Chem.	W. Germany	1978
Corpormon	Nikken	Japan	–
Somacton	Ferring	W. Germany	–
Somatormone	Byla	France	–

Raw Materials

Human pituitary glands
Acetone

Manufacturing Process

It has been found that the growth hormone can be obtained in crystalline form from human pituitary glands by procedures comprising (1) extraction of the fresh glands with acetone, (2) extraction of the acetone residue with aqueous salt solutions, (3) precipitation from aqueous salt solutions by the addition of suitable miscible organic solvents of alkaline and acid pH, and finally crystallization from aqueous salt solutions by the addition of suitable miscible organic solvents.

References

Merck Index 8562
DOT 14 (9) 422 (1978)
I.N. p. 880
REM pp. 952, 955
Lewis, U.J. and Brink, N.G.; U.S. Patent 2,974,088; March 7, 1961; assigned to Merck & Co., Inc.

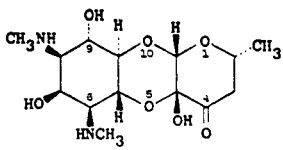
SPECTINOMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)-4H-pyrano-[2,3-b] [1,4] benzodioxin-4-one

Common Name: Actinospectacin

Structural Formula:



Chemical Abstracts Registry No.: 1695-77-8; 22189-32-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Trobicin	Upjohn	U.S.	1971
Trobicin	Upjohn	Italy	1973
Stanilo	Upjohn	W. Germany	1973

Trade Name	Manufacturer	Country	Year Introduced
Trobicin	Upjohn	U.K.	1973
Trobicine	Upjohn	France	1974
Trobicin	Upjohn	Japan	1978
Kempi	Alter	Spain	—

Raw Materials

Bacterium *Streptomyces spectabilis*
Nutrient medium

Manufacturing Process

A lyophilized culture of *Streptomyces spectabilis,* NRRL 2792, was used to seed the following sterile agar medium on tubed slants:

	Grams
Maltose	10
Tryptone	5
K_2HPO_4	0.5
NaCl	0.5
$FeSO_4$	0.1
Agar	20
Deionized water to make 1 liter	

The slants were incubated for 7 days at 30°C, after which time sporulation was complete. The spores from the agar slants were used, in an aqueous suspension, to inoculate 100 ml of preseed medium in a 500 ml Erlenmeyer flask. The sterile preseed medium consisted of:

	Grams
Dried whole yeast	10
Glucose	10
Pancreatic digest of casein (N-Z-Amine B)	5
Tap water to make 1 liter adjusted to pH 7.2 before sterilizing	

The seed flash was incubated for 24 hours at 32°C on a reciprocating shaker after which it was used as an inoculum for a 20 liter seed fermenter in the amount of approximately 5%. the 20 liter seed fermenter contained a sterile medium consisting of:

	Grams
Glucose	15
Cornstarch	25
Distiller's solubles	15
Brewer's yeast	10
Corn steep liquor	20
Tap water to make 1 liter adjusted to pH 7.2 before sterilizing	

The 20 liter seed fermenter was incubated for 24 hours at 32°C and aerated at the rate of 6 standard liters or about 0.2 standard cubic feet of air per minute and agitated with a sweep stirrer. The 20 liter seed fermenter was used to inoculate 250 liters of the same medium in a 100 gallon fermentation tank. 1,200 ml of lard oil were added during the fermentation to control foaming. The tank was agitated with a propeller and aerated at the rate of 75 standard liters of air per minute. After 96 hours of fermentation the beer assayed 500 mcg/ml (18.3 mcg/mg on a dry basis) of actinospectacin. Actinospectacin is assayed by its activity against *Klebsiella pneumoniae* by standard agar diffusion procedure and based on crystalline actinospectacin sulfate according to U.S. Patent 3,234,092.

References

Merck Index 8584
Kleeman & Engel p. 821
PDR p. 1864
DOT 8 (3) 107 (1972)
I.N. p. 884
REM p. 1211
Jahnke, H.K.; U.S. Patent 3,206,360; September 14, 1965; assigned to The Upjohn Co.
Bergy, M.E. and De Boer, C.; U.S. Patent 3,234,092; February 8, 1966; assigned to The Upjohn Company
Peters, V.J.; U.S. Patent 3,272,706; September 13, 1966; assigned to The Upjohn Company
Nara, T., Takasawa, S., Okachi, R., Kawamoto, I., Kumakawa, M., Yamamoto, M. and Sato, S.; U.S. Patent 3,819,485; June 25, 1974; assigned to Abbott Laboratories

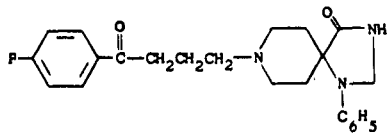
SPIPERONE

Therapeutic Function: Tranquilizer

Chemical Name: 8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 749-02-0

Trade Name	Manufacturer	Country	Year Introduced
Spiropitan	Eisai	Japan	1969
Spiroperidol	Janssen	–	–

Raw Materials

4-Carbamoyl-4-N-anilinopiperidine
Formamide
4-Chloro-p-fluoro-butyrophenone

Manufacturing Process

A mixture of 4-carbamoyl-4-N-anilinopiperidine and formamide is heated for 12 hours at 170°C. After cooling, the reaction mixture is divided between 100 parts water and 900 parts chloroform. The organic layer is separated, dried over $MgSO_4$, filtered and the filtrate is evaporated. The semisolid residue is stirred in ethyl acetate. The undissolved part is filtered off, washed with ethyl acetate, and dried, yielding 1-oxo-4-phenyl-2,4,8-triazaspiro-(4.5)decane.

A mixture of 3.2 parts 4-chloro-p-fluoro-butyrophenone, 3.5 parts 1-oxo-4-phenyl-2,4,8-triazaspiro(4.5)decane, 2 parts Na_2CO_3 and 0.1 part KI in 200 parts hexone is refluxed with stirring for 50 hours. The mixture is cooled to room temperature, 200 parts water are added and the layers are separated. The organic layer is dried over 10 parts $MgSO_4$,

filtered and the solvent removed under reduced pressure on the water bath. The residue is treated with 50 parts diisopropylether. The precipitate is filtered on a Buchner filter and recrystallized from 20 parts hexone at room temperature. The solid is filtered off and dried to yield 1-oxo-4-phenyl-8-[3-(4-fluorobenzoyl)-propyl] -2,4,8-triazaspiro(4.5)decane, melting point 190° to 193.6°C, as a light brown amorphous powder.

References

Merck Index 8596
Kleeman & Engel p. 821
I.N. p. 885
Janssen, P.A.J.; U.S. Patent 3,155,669; November 3, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; U.S. Patent 3,155,670; November 3, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; U.S. Patent 3,161,644; December 15, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium

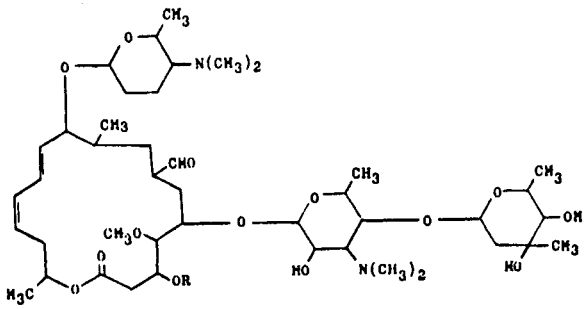
SPIRAMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Spiramycin

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 8025-81-8

Trade Name	Manufacturer	Country	Year Introduced
Rovamycine	Specia	France	1972
Rovamycina	Carlo Erba	Italy	1979
Apyrectol Spiramycine	Theranol	France	–
Bykomycetin	Byk Gulden	–	–
Selectomycin	Gruenenthal	W. Germany	–
Spiramycin	Kyowa	Japan	–

Raw Materials

Bacterium *Streptomyces ambofaciens*
Nutrient medium

Manufacturing Process

The process for producing spiramycin comprises inoculating an aqueous nutrient medium with a culture of the NRRL No. 2420, allowing aerobic fermentation to take place and separating from the culture medium the spiramycin thus formed. The culture medium also contains the antibiotic substance known as Congocidin which, however, does not possess the same useful properties as spiramycin and which can be isolated in crystalline form. The separation of the two antibiotic substances is readily achieved.

References

Merck Index 8597
Kleeman & Engel p. 822
I.N. p. 885
REM p. 1224

Ninet, L. and Verrier, J.; U.S. Patent 2,943,023; June 28, 1960; assigned to Societe des Usines Chimiques Rhone-Poulenc

Ninet, L., Pinnert S. and Preud'homme, J.; U.S. Patent 3,000,785; September 19, 1961; assigned to Societe des Usines Chimiques Rhone-Poulenc

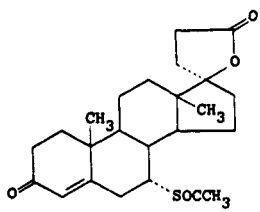
SPIRONOLACTONE

Therapeutic Function: Diuretic

Chemical Name: 7α-(acetylthio)-17α-hydroxy-3-oxopregn-4-ene-21-carboxylic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 52-01-7

Trade Name	Manufacturer	Country	Year Introduced
Aldactone	Searle	U.S.	1959
Aldactone	Searle	France	1960
Altex	Cenci	U.S.	1980
Diatensec	Searle	U.K.	1981
Acelat	Endopharm	W. Germany	—
Airolactone	Horita	Japan	—
Aldactazide	Searle	U.S.	—
Aldopur	Heumann	W. Germany	—
Aldospirone	Teva	Israel	—
Alexan	Sanwa	Japan	—
Almatol	Fujisawa	Japan	—
Alpamed	Sawai	Japan	—
Alpolasnon	Nihon Yakuhin	Japan	—
Aporasnon	Nichiiki	Japan	—
Dairopeal	Daito Koeki	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Deverol	Waldheim	Austria	–
Dira	Kakenyaku Kako	Japan	–
Duraspiron	Durachemie	W. Germany	–
Euteberol	Merckle	W. Germany	–
Hokulaton	Hokuriku	Japan	–
Idrolattone	Zoja	Italy	–
Lacalmin	Tatsumi	Japan	–
Lacdene	Tsuruhara	Japan	–
Nefurofan	Maruko	Japan	–
Osyrol	Hoechst	W. Germany	–
Penantin	Teikoku	Japan	–
Practon	Genekod	France	–
Sagisal	Sagitta	W. Germany	–
Sincomen	Schering	W. Germany	–
Spiresis	Farmos	Finland	–
Spiretic	D.D.S.A.	U.K.	–
Spiridon	Orion	Finland	–
Spirix	Benzon	Denmark	–
Spirolong	SKF	Italy	–
Spironazide	Schein	U.S.	–
Spiropal	A.F.I.	Norway	–
Spiro-Tablinen	Sanorania	W. Germany	–
Spirotone	Protea	Australia	–
Suracton	Toho Iyaku	Japan	–
Uractone	Spa	Italy	–
Urosonin	Isei	Japan	–
Xenalone	Mepha	Switz.	–

Raw Materials

17α-(2-Carboxyethyl)-17β-hydroxyandrosta-4,6-dien-3-one lactone
Thioacetic acid

Manufacturing Process

A mixture of approximately 11 parts of 17α-(2-carboxyethyl)-17β-hydroxyandrosta-4,6-dien-3-one lactone and 10 parts of thioacetic acid is heated at 85° to 95°C for ½ hour. Excess thioacetic acid is removed by vacuum distillation at this point, and the residue is twice recrystallized from methanol, affording 7α-acetylthio-17α-(2-carboxyethyl)-17β-hydroxyandrost-4-en-3-one lactone, melting at approximately 134° to 135°C. Heated above this melting point, the product solidifies and melts again at approximately 201° to 202°C (with decomposition).

References

Merck Index 8610
Kleeman & Engel p. 822
PDR pp. 830, 993, 1388, 1606, 1674, 1999
OCDS Vol. 1 p. 206 (1977); 2, 172 (1980) & 3, 91 (1984)
I.N. p. 886
REM p. 941
Cella, J.A. and Tweit, R.C.; U.S. Patent 3,013,012; December 12, 1961; assigned to G.D. Searle & Co.

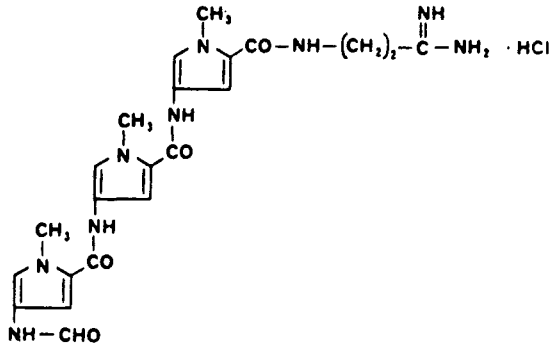
STALLIMYCIN HYDROCHLORIDE

Therapeutic Function: Antibiotic

Chemical Name: N''-(2-Amidinoethyl)-4-formamido-1,1',1''-trimethyl-N,4':N',4''-ter-(pyrrole-2-carboxamide) hydrochloride

Common Name: Distamycin A

Structural Formula:



Chemical Abstracts Registry No.: 6576-51-8; 636-47-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Herperal	Farmitalia	Italy	1978

Raw Materials

Bacterium *Streptomyces distallicus*
Dextrose
Corn steep liquor

Manufacturing Process

A spore suspension obtained upon washing a culture of *Streptomyces distallicus* is added to 3,000 ml of a sterile medium consisting of the following:

Dextrose	2 %
Corn steep liquor extract	2 %
$CaCO_3$	1 %
$(NH_4)_2SO_4$	0.3 %
NaCl	0.3 %

Fermentation is continued at 28°C for 40 hours at a stirring rate of 150 to 250 rpm and a rate of air flow of 1 to 2 ℓ/min/ℓ of culture medium.

300 ml of a suspension of the vegetative mycelium of this culture are used for inoculating 6,000 ml of a similar sterile culture medium. At this production stage, the culture is kept fermenting for 85 to 100 hours (pH 7.6 at 28°C) at a stirring rate of 350 to 450 rpm and a rate of air flow of 1 to 1.5 ℓ/min/ℓ of culture medium.

To 17 ℓ of a culture obtained by submerged fermentation as mentioned above, siliceous earth is added and the batch is filtered. The mixture of mycelium and the siliceous earth are agitated for 1 hour with 2.5 ℓ of butanol. This treatment is repeated twice. The butanolic extracts are combined, washed with water, evaporated to dryness (about 10 g) and boiled with acetone (80 ml). The residue (5.41 g of yellowish powder) is distamycin.

5 g of distamycin is extracted six times with ethanol. The ethanolic extracts are combined, concentrated and filtered through a column containing 70 g of alumina. Elution is carried

out with the same solvent. The effluent (central fractions) is collected and evaporated to dryness to yield 0.43 g of pure distamycin A: decomposition point, 183°C to 185°C. The product can be further purified by crystallization from aqueous n-butanol.

References

Merck Index 8623
Kleeman & Engel p. 824
DOT 13 (8) 322 (1977)
I.N. p. 887
Arcamone, F., Canevazzi, G., Grein, A. and Bizioli, F.; U.S. Patent 3,190,801; June 22, 1965; assigned to Societa Farmaceutici Italia

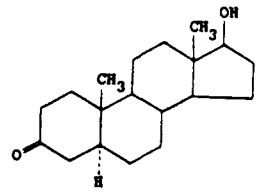
STANOLONE

Therapeutic Function: Androgen

Chemical Name: 17-Hydroxyandrostan-3-one

Common Name: Androstanolone

Structural Formula:



Chemical Abstracts Registry No.: 521-18-6

Trade Name	Manufacturer	Country	Year Introduced
Neodrol	Pfizer	U.S.	1953
Anabolex	Lloyd	U.K.	—
Anaprotin	Cuxson	U.K.	—
Androlone	Orma	Italy	—
Ophthovitol	Winzer	W. Germany	—
Pesomax	Boniscontro	Italy	—
Protona	Gremy-Longuet	France	—
Stanaprol	Pfizer	—	—

Raw Materials

3,17-Androstandione
Selenium dioxide
Sodium borohydride

Manufacturing Process

A solution of 1.0 g of 3,17-androstandione in 50 ml of methanol and containing 1 g of selenium dioxide, was allowed to remain in an ice-chest overnight. The formed 3,3-dimethoxy-androstan-17-one was not separated. 1 g of solid potassium hydroxide and 2.5 g of sodium borohydride in 2.5 ml of water were added and the mixture allowed to react at room temperature for 24 hours. The solution was then poured into a large excess of water, extracted

with methylene chloride, the organic layer dried and evaporated to a residue. The residue was dissolved in ether, and a small amount of selenium removed by filtration. The ether was boiled off and the organic material dissolved in 100 ml of boiling acetone. 25 ml of diluted hydrochloric acid were added, the solution boiled for 5 minutes and then allowed to cool. Upon crystallization, 0.85 g of androstan-17β-ol-3-one was obtained, melting point 175°C to 178°C.

References

Merck Index 8646
Kleeman & Engel p. 54
I.N. p. 88
Oliveto, E.P. and Hershberg, E.B.; U.S. Patent 2,927,921; March 8, 1960; assigned to Schering Corp.

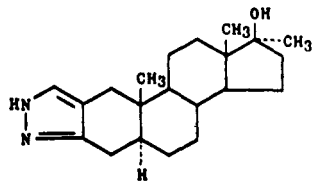
STANOZOLOL

Therapeutic Function: Anabolic

Chemical Name: 17-methyl-2H-5α-androst-2-eno[3,2-c] pyrazol-17β-ol

Common Name: Androstanazole

Structural Formula:



Chemical Abstracts Registry No.: 10418-03-8

Trade Name	Manufacturer	Country	Year Introduced
Winstrol	Winthrop	U.S.	1961
Strombaject	Winthrop	W. Germany	1961
Stromba	Sterling	U.K.	1961
Winstol	Zamba	Italy	1962
Stromba	Winthrop	France	1964
Anasynth	Causyth	Italy	–

Raw Materials

17β-Hydroxy-17α-methyl-4-androsteno[3,2-c] pyrazole
Lithium
Ammonia

Manufacturing Process

To a stirred solution of 1.00 gram of 17β-hydroxy-17α-methyl-4-androsteno[3,2-c] pyrazole in 200 ml of tetrahydrofuran and 400 ml of liquid ammonia was added 2.12 grams of lithium wire during 5 minutes. The dark blue mixture was stirred for 45 minutes. A solution of 40 ml of tertiary-butyl alcohol in 160 ml of diethyl ether was added with stirring.

After 15 minutes, 25 ml of ethanol was added with stirring. The mixture turned colorless after several hours, and the liquid ammonia was allowed to evaporate and the mixture was allowed to warm to room temperature over a period of about 15 hours.

The solvent was evaporated to yield a colorless solid residue, which was taken up in ethyl acetate-ice water. The two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, saturated sodium chloride solution and filtered through anhydrous sodium sulfate. The solvent was evaporated to yield 1.20 grams of light tan crystals, MP 151° to 155°C, ultraviolet maximum at 224 mμ (E = 4,095). Two recrystallizations from ethanol afforded: 1st crop, 0.619 grams (62%) of colorless crystals (dried at 120°C in vacuo for 17 hours), MP 232.8° to 238.0°C, ultraviolet maximum at 224 mμ (E = 4,840); 2nd crop, 0.142 gram (14%) of colorless crystals, MP 234° to 242°C.

References

Merck Index 8647
Kleeman & Engel p. 825
PDR p. 1935
DOT 15 (6) 278 (1979)
I.N. p. 888
REM p. 1000
Manson, A.J.; U.S. Patent 3,030,358; April 17, 1962; assigned to Sterling Drug Inc.

STREPTOKINASE

Therapeutic Function: Enzyme

Chemical Name: Streptococcal fibrinolysin

Common Name: —

Structural Formula: Complex enzyme mixture

Chemical Abstracts Registry No.: 9002-01-1

Trade Name	Manufacturer	Country	Year Introduced
Streptase	Hoechst	France	1970
Streptase	Hoechst	U.S.	1977
Kabikinase	Kabi	U.S.	1980
Awelysin	Arzneimittelwerk Dresden	E. Germany	—
Varidase	Lederle	U.K.	—

Raw Materials

Bacterium *Streptococcus haemolyticus*
Nutrient medium

Manufacturing Process

The following description is from U.S. Patent 2,701,227: To 50 liters of distilled water there was added 10.17 kg of enzyme hydrolyzed casein (N-Z-Amine). The temperature was raised to 100°C and held until the casein digest solution was clear. The container was then cooled rapidly to 15°C and the cooled solution filtered through a coarse grade of filter paper. A small amount of toluene was added as a preservative and the solution

stored at 2°C for 4 days, at the end of which time it was again filtered to remove any insoluble material.

The following ingredients were then added to the casein digest solution: 1,165.0 grams of KH_2PO_4 dissolved in 8 liters of distilled water; 35.0 grams of cysteine in approximately 800 cc of 10% HCl (the least amount of 10% HCl required to obtain a clear solution); 35 grams of glycine dissolved in 100 cc of distilled water; 300 grams dextrose in 2 liters of distilled water; 3.5 grams of uracil in 1 liter of distilled water; 3.5 grams of adenine sulfate in 1 liter of distilled water; 0.35 gram of nicotinic acid in 35 cc of distilled water; 0.59 gram of pyridoxine dissolved in 59 cc of distilled water; 7.0 grams of tryptophane in 1 liter of distilled water; 1.75 grams of calcium pantothenate in 70 cc of distilled water; 0.875 gram of thiamin hydrochloride dissolved in 87.5 cc of distilled water; 0.175 gram of riboflavin dissolved in 1,000 cc of distilled water; 55.65 cc of thioglycollic acid in 100 cc of distilled water; 700 grams of $KHCO_3$ in 500 cc of distilled water and 700 cc of a trace element salt solution containing 11.5 kg of $MgSO_4$; 50 g of $CuSO_4 \cdot 5H_2O$; 50 g of $ZnSO_4 \cdot 7H_2O$; 20 g $MnCl_2 \cdot 4H_2O$; 50 g of $FeSO_4 \cdot 7H_2O$; 1 liter of HCl per 100 liters of solution. The medium was then adjusted to pH 7.2 and sterilized by filtration.

The above sterilized medium was inoculated with 11 liters of seed inoculum having a bacterial count of approximately 20 billion per cc. The tank was fermented at 37°C without pH adjustment, aeration, or other modification for 14 hours at the end of which time 320 cc of 50% dextrose was added. After this the pH was adjusted to 7.0 at 15 minute intervals with 5.0 N sodium hydroxide. The volume of sodium hydroxide required for neutralization was noted and 115% of this volume of 50% dextrose solution added after each pH adjustment. At the end of about 8 hours the bacterial count had ceased to increase and the fermentation was terminated. At this time the fermentation medium contained approximately 1,000 units of streptokinase per cc.

References

Merck Index 8683
Kleeman & Engel p. 826
PDR pp. 944, 963, 1428
I.N. p. 891
REM p. 1037
Ablondi, F.B. and Adam, J.N. Jr.; U.S. Patent 2,701,227; February 1, 1955; assigned to American Cyanamid Company
Mowat, J.H., Krupka, G.C. and Nalesnyk, S.; U.S. Patent 2,753,291; July 3, 1956; assigned to American Cyanamid Company
Singher, H.O. and Zuckerman, L.; U.S. Patent 3,016,337; January 9, 1962; assigned to Ortho Pharmaceutical Corporation
Siegel, M., Palombo, G. and Baumgarten, W.; U.S. Patent 3,042,586; July 3, 1962; assigned to Merck & Co., Inc.
von Pölnitz, W., Schwick, H.G. and Bickhard, J.H.; U.S. Patent 3,063,913; November 13, 1962; assigned to Behringwerke AG, Germany
von Pölnitz, W., Schwick, H.G. and Bickhard, J.H.; U.S. Patent 3,063,914; November 13, 1962; assigned to Behringwerke AG, Germany
Baumgarten, W. and Cole, R.B.; U.S. Patent 3,107,203; October 15, 1963; assigned to Merck & Co., Inc.
von Pölnitz, W., Schwick, H.G. and Bickhard, J.H.; U.S. Patent 3,138,542; June 23, 1964; assigned to Behringwerke AG, Germany

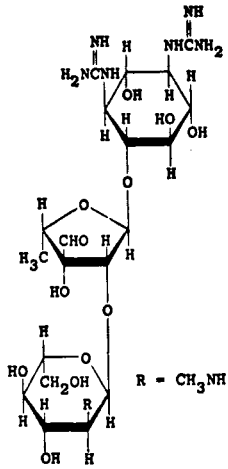
STREPTOMYCIN

Therapeutic Function: Antitubercular

Chemical Name: O-2-deoxy-2-(methylamino)-α-L-glucopyranosyl-(1→2)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(1→4)-N,N'-bis(aminoiminomethyl)-D-streptamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57-92-1

Trade Name	Manufacturer	Country	Year Introduced
Streptomycin	MSD	U.S.	1945
Streptomycine	Diamant	France	1961
Cidan-Est	Cidan	Spain	–
Darostrep	SCS Pharmalab	S. Africa	–
Estrepto E	Wassermann	Spain	–
Estrepto Level	Level	Spain	–
Estreptomicina	Cepa	Spain	–
Estreptomicina Normon	Normon	Spain	–
Estrepto Wolner	Wolner	Spain	–
Estreptomade	Made	Spain	–
Neodiestostreptobap	Martin Santos	Spain	–
Orastrep	Dista	U.K.	–
Servistrep	Servipharm	Switz.	–
Solvo-Strep	Heyl	W. Germany	–
Streptaguaine	Dista	U.K.	–
Streptobretin	Norbrook	U.K.	–
Streptosol	Therapex	Canada	–
Strycin	Squibb	U.S.	–

Raw Materials

Bacterium *Streptomyces griseus*
Nutrient medium

Manufacturing Process

A medium is prepared having the following composition in tap water: 1.0% glucose; 0.5% peptone; 0.3% meat extract; and 0.5% NaCl. This medium is distributed in appropriate vessels to a depth of 1 to 2 inches, sterilized at 10 pounds steam pressure for 45 to 50 minutes, and then cooled.

The medium in each vessel is then inoculated with a heavy aqueous suspension of spores of a strain of *Actinomyces griseus,* and the inoculated media are maintained at an incubation temperature of 22° to 28°C for 10 days. The growth is then filtered off and the filtrates are combined for further treatment.

To a batch of approximately 10 liters of filtered broth is added 150 grams of activated charcoal. The mixture is stirred continuously for about 5 minutes and is then filtered. The slightly yellowish (almost colorless) filtrate is discarded and the charcoal residue is washed several times with distilled water and finally with 95% ethanol. The washed material is then suspended in 1.5 liters of 95% ethanol, made 0.15 normal with hydrochloric acid. The suspension is stirred for about an hour and allowed to stand in the cold for about 10 hours more with occasional stirring. The suspension is then filtered, the charcoal residue discarded, and the yellowish clear filtrate thus obtained is poured into 10 liters of ether, with stirring. A brown-colored aqueous layer separates and is drawn off.

The alcohol-ether solution is washed with 100 cc of water and the brown aqueous layer is drawn off and added to the first aqueous layer. The aqueous solution is neutralized to pH 6 to 7 with dilute sodium hydroxide and any precipitate that forms is filtered off and discarded. A faintly colored aqueous solution containing streptomycin is thus obtained.

References

Merck Index 8685
Kleeman & Engel p. 827
PDR p. 1410
I.N. p. 892
REM p. 1260
Waksman, S.A. and Schatz, A.; U.S. Patent 2,449,866; September 21, 1948; assigned to Rutgers Research and Endowment Foundation
Bartels, C.R., Bryan, W.L. and Berk, B.; U.S. Patent 2,868,779; January 13, 1959; assigned to Olin Mathieson Chemical Corporation

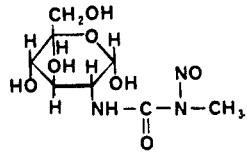
STREPTOZOCIN

Therapeutic Function: Antineoplastic

Chemical Name: 2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 18883-66-4

Trade Name	Manufacturer	Country	Year Introduced
Zanosar	Upjohn	U.S.	1982

Raw Materials

Bacterium *Streptomyces achromogenes*
Nutrient medium

Manufacturing Process

On a sterile maltose-tryptone agar slant of the following composition: 1 g maltose; 0.5 g tryptone; 0.05 g K_2HPO_4; 0.01 g $FeSO_4 \cdot 7H_2O$; 1.5 g agar; and sufficient distilled water to make 100 ml, *Streptomyces achromogenes* var. *streptozoticus* was grown for 7 days at 28°C.

The culture thus produced was used as an inoculum for the following sterile medium: 1 g glucose; 1 g beef extract; 0.5 g Bacto peptone (Difco); 0.5 g NaCl; and sufficient distilled water to make 100 ml. The pH was adjusted to 7.0 before sterilization. The inoculated medium was incubated in shake flasks for 3 days at 28°C on a reciprocating shaker and 75 ml of the resulting growth was used to inoculate 12 ℓ of sterile medium of the same formulation. The medium was incubated in a 20 ℓ stainless steel bottle, at 28°C for 2 days, the contents being stirred continuously with sparged air at the rate of 6 ℓ of free air per minute. The resulting growth was used to inoculate 250 ℓ of the following sterile medium: 2 g Bacto peptone (Difco); 2.5 g blackstrap molasses; 2 g glucose; 0.25 g NaCl; and sufficient distilled water to make 100 ml. The pH was adjusted to 7.0 before sterilization.

This medium was incubated in a 100 gallon stainless steel fermentor, at 24°C with sparged air being introduced at the rate of 50 ℓ/min and with agitation by an impeller. After 66 hours of fermentation the beer was harvested. To 100 gallons of harvested beer was added 17 pounds of diatomite, and 35 pounds of activated carbon. The mixture was stirred well and then filtered, the cake was water-washed with 10 gallons of tap water, and then washed with 25 gallons of acetone followed by 30 gallons of 1:1 aqueous acetone. The acetone solutions of streptozotocin were pooled and dried in vacuo to 3.88 pounds.

References

Merck Index 8695
DFU 4 (2) 137 (1979)
DOT 19 (5) 242 (1983)
I.N. p. 892
REM p. 1156
Bergy, M.E., De Boer, C., Dietz, A., Eble, T.E., Herr, R.R. and Johnson, L.E.; U.S. Patent 3,027,300; March 27, 1962; assigned to The Upjohn Co.

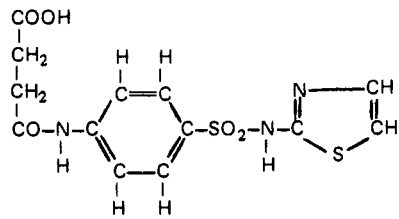
SUCCINYLSULFATHIAZOLE

Therapeutic Function: Antibacterial (intestinal)

Chemical Name: 4-Oxo-4[[4-[(2-thiazolylamino)-sulfonyl] phenyl] amino] butanoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 116-43-8

Trade Name	Manufacturer	Country	Year Introduced
Sulfasuxidine	MSD	U.S.	1942
Thiacyl	Theraplix	France	1946
Colistatin	Smith & Nephew	U.K.	–
Cremosuxidine	MSD	U.K.	–

Raw Materials

2-Sulfanilamidothiazole
Succinic anhydride

Manufacturing Process

3.92 g of succinic anhydride was added to a boiling suspension of 10 g of 2-sulfanilamidothiazole in 100 cc of alcohol. The mixture was then refluxed for five minutes after the addition was complete at which time all of the solids were in solution. The solution was then cooled and diluted with an equal volume of water. The white solid precipitate which formed was filtered and recrystallized from dilute alcohol, yielding 2-N^4-succinylsulfanilamidothiazole, melting at 184°C to 186°C.

References

Merck Index 8753
Kleeman & Engel p. 831
OCDS Vol. 1 p. 132 (1977)
I.N. p. 894
Moore, M.L.; U.S. Patents 2,324,013 and 2,324,014; both dated July 13, 1943; assigned to Sharp & Dohme, Inc.

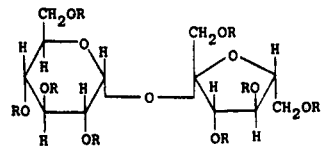
SUCRALFATE

Therapeutic Function: Antiulcerative

Chemical Name: Hexadeca-μ-hydroxytetracosahydroxy[μ_8-[1,3,4,6-tetra-O-sulfo-β-D-fructofuranosyl-α-D-glucopyranoside tetrakis(hydrogen sulfato)(8-)]]hexadecaaluminum

Common Name: –

Structural Formula:



R = $SO_3[Al_2(OH)_5]$

Chemical Abstracts Registry No.: 54182-58-0

Trade Name	Manufacturer	Country	Year Introduced
Antepsin	Baldacci	Italy	1975
Ulcogant	Cascan	W. Germany	1980
Carafate	Marion	U.S.	1981
Ulogant	Merck	Switz.	1982

Trade Name	Manufacturer	Country	Year Introduced
Antepsin	Ayerst	U.K.	1982
Ulsanic	DuPont	Australia	1983
Andapsin	Farmos	Sweden	1983
Sulcrate	Nordic	Canada	—
Ulcerlmin	Chugai	Japan	—

Raw Materials

Sulfur trioxide
Sucrose
Aluminum dihydroxychloride
Pyridine
Sodium hydroxide

Manufacturing Process

A disaccharide is added to a pyridine SO_3 complex solution, which is prepared by reacting 5 to 6 times the molar amount of liquid SO_3 as much as that of disaccharide with 5 to 10 times the amount of pyridine as that of the disaccharide at 0°C to 5°C, for sulfation at 50°C to 70°C for 3 to 7 hours. After the completion of sulfation, the greater part of pyridine is removed by decantation. The obtained solution exhibits an acidity that is so strong that it is improper to apply the reaction with aluminum ion and, therefore, sodium hydroxide is added for neutralization. After the remaining pyridine is removed by concentration, 100 unit volumes of water per unit volume of the residue is added thereto. To the solution is then added aluminum ion solution mainly containing aluminum dihydroxychloride, the pH of which is 1.0 to 1.2, in such an amount that the aluminum ion is present in an amount of 4 to 6 molar parts of the amount of disaccharide to provide a pH of 4 to 4.5. The mixture is reacted under stirring at room temperature and the formed disaccharide polysulfate-aluminum compound is allowed to precipitate. After filtration, the residue is washed with water and dried.

References

Merck Index 8755
PDR p. 1074
I.N. p. 894
REM p. 815
Nitta, Y., Namekata, M., Tomita, E. and Hirota, Y.; U.S. Patent 3,432,489; March 11, 1969; assigned to Chugai Seiyaku K.K. (Japan)

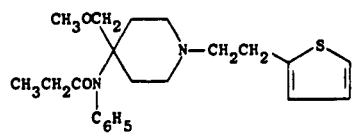
SUFENTANIL

Therapeutic Function: Analgesic

Chemical Name: N-[4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: —

Trade Name	Manufacturer	Country	Year Introduced
Sufenta	Janssen	Neth.	1983
Sufenta	Janssen	U.S.	—

Raw Materials

N-[4-(Methoxymethyl)-4-piperidinyl] -N-phenylpropanamide
2-Thiopheneethanol

Manufacturing Process

A mixture of 4.1 parts of N-[4-(methoxymethyl)-4-piperidinyl] -N-phenylpropanamide, 5.3 parts of sodium carbonate and 120 parts of 4-methyl-2-pentanone is stirred and refluxed with water-separator. Then there are added 4.1 parts of 2-thiopheneethanol methanesulfonate ester and stirring at reflux is continued for 18 hours. The reaction mixture is cooled, washed twice with water and evaporated. The oily residue is purified by column-chromatography over silica gel, using a mixture of trichloromethane and 5% of methanol as eluent. The first fraction is collected and the eluent is evaporated. The oily residue is converted into the hydrochloride salt in 2,2'-oxybispropane. The free base is liberated again in the conventional manner. After extraction with 2,2'-oxybispropane, the latter is dried, filtered and evaporated. The oily residue solidifies on triturating in petroleum-ether. The solid product is filtered off and crystallized from petroleum-ether at -20°C, yielding, after drying, N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl] -4-piperidinyl] -N-phenylpropanamide; melting point 98.6°C.

References

Merck Index A-12
DFU 2 (5) 334 (1977)
PDR p. 959
I.N. p. 895
Janssen, P.A.J. and Daele, H.P.V.; U.S. Patent 3,998,834; December 21, 1976; assigned to Janssen Pharmaceutica N.V. (Belgium)

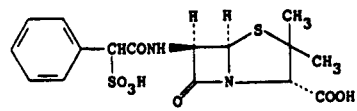
SULBENICILLIN

Therapeutic Function: Antibacterial

Chemical Name: 3,3-Dimethyl-7-oxo-6-[(phenylsulfoacetyl)amino] -4-thia-1-azabicyclo-[3.2.0] heptane-2-carboxylic acid

Common Name: Sulfocillin

Structural Formula:



Chemical Abstracts Registry No.: 41744-40-5; 28002-18-8 (Na salt)

Trade Name	Manufacturer	Country	Year Introduced
Lillacillin	Takeda	Japan	1973
Kedacillina	Bracco	Italy	1982

Raw Materials

α-Sulfophenacetyl chloride
6-Aminopenicillanic acid

Manufacturing Process

To a suspension of 1.08 parts by weight of 6-aminopenicillanic acid in 8 parts by volume of water is added 1.48 parts by weight of sodium bicarbonate. After the mixture is dissolved, a solution of 1.18 parts by weight of α-sulfophenylacetyl chloride in 10 parts by volume of diethylether is gradually added thereto. The mixture is stirred at a temperature in the neighborhood of 0°C for 1 hour. The aqueous layer is washed twice with 10 parts by volume of portions of ether and adjusted to pH 1.2 with cation exchange resin of polystyrene sulfonic acid type under constant cooling. Then the solution is washed twice with 15 parts by volume of portions of ethyl acetate, followed by extraction twice with 15 parts by volume of portions of n-butanol. The extracts are combined and washed twice with 15 parts by volume of portions of water and, then, extracted with an aqueous solution of sodium bicarbonate. The extract is adjusted to pH 6.5, washed with ether and lyophilized to give the sodium salt of α-sulfobenzylpenicillin. Yield is 1.2 parts by weight.

References

Merck Index 8762
DOT 8 (5) 199 (1972) & 9 (4) 149 (1973)
I.N. p. 895
REM p. 1201
Morimoto, S., Nomura, H., Fugono, T., Maeda, K. and Ishiguro, T.; U.S. Patent 3,600,379; May 2, 1972; assigned to Takeda Chemical Industries, Ltd. (Japan)

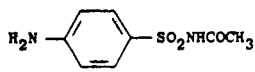
SULFACETAMIDE

Therapeutic Function: Antimicrobial

Chemical Name: N-[(4-aminophenyl)sulfonyl] acetamide

Common Name: N'-acetylsulfanilamide

Structural Formula:



Chemical Abstracts Registry No.: 144-80-9

Trade Name	Manufacturer	Country	Year Introduced
Sulamyd	Schering	U.S.	1941
Urosulfon	Consol. Midland	U.S.	1955
Sulfacidin	Crookes	U.K.	–
Sultrin	Ortho	U.S.	–
Triple Sulfa	Fougera	U.S.	–
Trysul	Savage	U.S.	–

Raw Materials

4-Aminobenzenesulfonamide
Acetic anhydride
Sodium hydroxide

Manufacturing Process

17.2 grams of 4-aminobenzene-sulfonamide are heated to boiling with 75 cc of acetic anhydride for 1 hour and thereupon the diacetyl product caused to separate by stirring into ice water. After recrystallization from alcohol the 4-acetylaminobenzene-sulfonacetyl-amide forms colorless prisms of melting point 253°C with decomposition. The product is easily soluble in alkalies and forms neutral salts. The acetylation can also take place with acetyl chloride. Instead of the 4-aminobenzene-sulfonamide also 4-acetylaminobenzene-sulfonamide can be employed. The action of 4-acetylaminobenzene-sulfonic acid chloride on acetamide yields the same product.

By heating the diacetyl compound with sodium hydroxide solution partial saponification of the acetyl groups takes place. 25.6 grams of diacetyl compound are heated to boiling for some hours with 100 cc of 2 N sodium hydroxide solution. The precipitate produced by acidification of the solution with acetic acid is filtered off and treated with dilute sodium carbonate solution. The 4-aminobenzene-sulfonacetylamide passes into solution while the simultaneously formed 4-acetylaminobenzene-sulfonamide remains undissolved. It is filtered with suction and the filtrate again acidified with acetic acid. The 4-aminobenzene-sulfonacetamide separates out and is recrystallized from water. It forms colorless lustrous rhombic crystals of MP 181°C.

References

Merck Index 100
Kleeman & Engel p. 833
PDR pp. 888, 1306, 1606
OCDS Vol. 1 p. 123 (1977)
I.N. p. 897
REM p. 1176
Dohrn, M. and Diedrich, P.; U.S. Patent 2,411,495; November 19, 1946; assigned to Schering Corporation

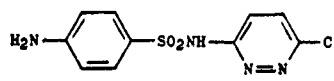
SULFACHLORPYRIDAZINE

Therapeutic Function: Antibacterial

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

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 80-32-0

Trade Name	Manufacturer	Country	Year Introduced
Sonilyn	Mallinckrodt	U.S.	1962
Nefrosul	Riker	U.S.	1974
Consulid	Ciba-Geigy	U.S.	–
Cosulfa	Elliott-Marion	Canada	–
Durasulf	Dessy	Italy	–
Sulfaclorazina	Ellem	Italy	–

Raw Materials

3,6-Dichloropyridazine
Sulfanilamide

Manufacturing Process

1.9 parts of 3,6-dichloropyridazine, 3.4 parts of sulfanilamide, 2.7 parts of potassium carbonate and 1 part of sodium chloride were ground together. The solid mixture was heated with stirring and as the dichloropyridazine and sulfanilamide melted, the mixture became a slurry. When the bath temperature had reached 140°C a sudden evolution of carbon dioxide occurred which lasted about 5 minutes, after which the mixture set in fine granules. When no more carbon dioxide was evolved, heating was stopped and the reaction mixture was heated with sufficient water to dissolve it and the solution allowed to cool. Unreacted sulfanilamide was collected by filtration. Excess dichloropyridazine was removed from the filtrate by extraction with a water immiscible organic solvent such as ether.

The basic solution was chilled and poured into one-half volume of 1:3 acetic acid. Sufficient hydrochloric acid was added to bring the mixture to pH 4. The crude 3-sulfanilamido-6-chloropyridazine which precipitated was purified by solution in 6 parts of 1:100 ammonium hydroxide, charcoal treatment and precipitation by pouring of the filtrate into dilute acetic acid.

References

Merck Index 8770
Kleeman & Engel p. 833
OCDS Vol. 1 pp. 124, 131 (1977)
I.N. p. 897
Lester, M.M. and English, J.P.; U.S. Patent 2,790,798; April 30, 1957; assigned to American Cyanamid Company

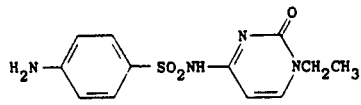
SULFACYTINE

Therapeutic Function: Antibacterial

Chemical Name: 4-(amino-N-(1-ethyl-1,2-dihydro-2-oxo-4-pyrimidinyl)benzenesulfonamide

Common Name: N-Sulfanilyl-1-ethylcytosine; sulfacitine

Structural Formula:



Chemical Abstracts Registry No.: 17784-12-2

Trade Name	Manufacturer	Country	Year Introduced
Renoquid	Glenwood	U.S.	1975
Renoquid	Parke Davis	U.S.	1983

Raw Materials

3-(Ethylamino)propionitrile
Sodium
Hydrogen bromide
N-Acetylsulfanilyl chloride
Potassium cyanate
Methanol
Bromine
Sodium hydroxide

Manufacturing Process

The N-(N-acetylsulfanilyl)-1-ethylcytosine used as a starting material is prepared as follows: To a solution of 333 grams of 3-(ethylamino)propionitrile in 1,697.3 ml of 2 N hydrochloric acid is added 275 grams of potassium cyanate, the resulting solution is concentrated under reduced pressure to a syrup, and the syrup is heated at 90° to 100°C for 6 hours and then evaporated to dryness at 90° to 100°C under reduced pressure. The residue is extracted with 1,600 ml of hot absolute ethanol, and the extract is concentrated to 500 ml and chilled. The crystalline 1-(2-cyanoethyl)-1-ethylurea obtained is isolated, washed with cold absolute ethanol, and dried, melting point 88° to 91°C. This intermediate (58.7 grams) is added to a solution of 11.5 grams of sodium in 500 ml of methanol and the resulting solution is heated under reflux for 30 minutes. After cooling, the mixture, containing 1-ethyl-5,6-dihydrocytosine, is treated with a slight excess of gaseous hydrogen bromide and evaporated to dryness. The residue is extracted, first with 500 ml, then with 100 ml of hot isopropyl alcohol, the extracts are combined and chilled, and the crystalline 1-ethyl-5,6-dihydrocytosine hydrobromide obtained is isolated and dried, MP 167.5 to 169.5°C. This salt (88.8 grams) is dissolved in 200 ml of nitrobenzene at 174°C, 22.6 ml of bromine is added over a period of 8 minutes, and the mixture is kept at 170° to 175°C until hydrogen bromide evolution ceases (about 15 minutes). Upon cooling, there is obtained crude 1-ethylcytosine hydrobromide, which is isolated, washed with ether, and dried, MP 170° to 187°C.

This salt is heated at 90° to 100°C with 70 ml of N,N-dimethylformamide and 60 ml of piperidine, and the resulting solution is chilled to give 1-ethylcytosine, MP 238° to 243°C. A mixture of 10.5 grams of 1-ethylcytosine, 18.6 grams of N-acetylsulfanilyl chloride, and 50 ml of pyridine is stirred at room temperature for 2 days. The precipitated solid is removed by filtration, and the filtrate is evaporated at 60°C under reduced pressure to a syrup. The syrup is triturated with 0.25 N hydrochloric acid, and the solid N-(N-acetylsulfanilyl)-1-ethylcytosine obtained is isolated and dried. This solid is suitable for use without further purification.

A solution of 65 grams of N-(N-acetylsulfanilyl)-1-ethylcytosine in 380 ml of 2 N aqueous sodium hydroxide is heated under reflux for 1 hour. Upon cooling, the solution is treated with charcoal, purified by filtration, and acidified with acetic acid. The solid N-sulfanilyl-1-ethylcytosine that precipitates is isolated, washed with water, and dried, MP 166.5° to 168°C following successive crystallizations from butyl alcohol and from methanol.

References

Merck Index 8771
Kleeman & Engel p. 834
PDR p. 926
OCDS Vol. 2 p. 113 (1980)
DOT 12 (9) 370 (1976)
I.N. p. 898
REM p. 1172
Doub, L. and Krolls, U.; U.S. Patent 3,375,247; March 26, 1968; assigned to Parke, Davis & Company

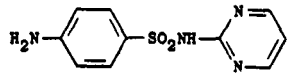
SULFADIAZINE

Therapeutic Function: Antibacterial

Chemical Name: 4-amino-N-2-pyrimidinylbenzenesulfonamide

Common Name: Sulfanilylaminopyrimidine; sulfapyrimidine

Structural Formula:



Chemical Abstracts Registry No.: 68-35-9

Trade Name	Manufacturer	Country	Year Introduced
Sulfadiazine	Lederle	U.S.	1941
Adiazin	Star	Finland	–
Adiazine	Theraplix	France	–
Coco-Diazine	Lilly	U.S.	–
Di-Azu-Mul	First Texas	U.S.	–
Flamazine	Smith & Nephew	U.K.	–
Lipo-Diazine	Donley Evans	U.S.	–
Magmoid Sulfadiazine	Pitman-Moore	U.S.	–
Sulfadets	Dymond	Canada	–
Sulfolex	Medica	Finland	–
Theradia	Daiichi	Japan	–
Theradiazine	Daiichi	Japan	–
Ultradiazin	Atabay	Turkey	–

Raw Materials

2-Aminopyrimidine
p-Nitrobenzenesulfonyl chloride
Iron
Hydrogen chloride

Manufacturing Process

5.4 parts of 2-amino-pyrimidine were covered with 15 parts of anhydrous pyridine. The reaction mixture was treated with 14 parts of p-nitrobenzenesulfonyl chloride and the whole heated briefly on the steam bath and let stand 45 minutes at room temperature. To the reaction mixture were added 80 parts of hot alcohol and the precipitate was filtered off and washed with water. The solid was dissolved in dilute caustic solution and the solution was filtered, cooled and acidified. The 2-(p-nitrobenzenesulfonamido)-pyrimidine precipitated and was collected.

The crude 2-(p-nitrobenzenesulfonamido)-pyrimidine from the preceding step was suspended in 130 parts alcohol and 1.5 parts of concentrated hydrochloric acid were added. The suspension was then heated to reflux and 30 parts of iron powder were added with mechanical stirring. The mixture was refluxed and stirred for 24 hours with occasional addition of concentrated hydrochloric acid. The reaction mixture was then made slightly basic and filtered hot and the residues were extracted with several portions of boiling alcohol. The filtrate and wash solutions were combined and evaporated. The 2-(sulfanilamido)-pyrimidine was recrystallized from boiling water with decolorizing charcoal added, according to U.S. Patent 2,410,793.

References

Merck Index 8772
Kleeman & Engel p. 834
OCDS Vol. 1 p. 124 (1977)
DOT 16 (8) 261 (1980)
I.N. p. 898
REM p. 1173
Sprague, J.M.; U.S. Patent 2,407,966; September 17, 1946; assigned to Sharp & Dohme, Inc.
Winnek, P.S. and Roblin, R.O. Jr.; U.S. Patent 2,410,793; November 5, 1946; assigned to American Cyanamid Company