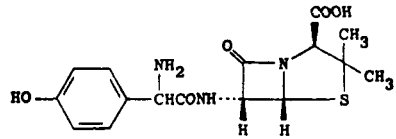
AMOXICILLIN

Therapeutic Function: Antibacterial

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

Common Name: p-Hydroxyampicillin

Structural Formula:



Chemical Abstracts Registry No.: 26787-78-0; 61336-70-7 (Trihydrate)

Trade Name	Manufacturer	Country	Year Introduced
Amoxil	Bencard	U.K.	1972
Clamoxyl	Beecham	W. Germany	1973
Clamoxyl	Beecham	France	1974
Larotid	Roche	U.S.	1974
Amoxil	Beecham	U.S.	1974
Polymox	Bristol	U.S.	1975
Sawacillin	Fujisawa	Japan	1975
Pasetocin	Kyowa Hakko	Japan	1975
Velamox	Zambeletti	Italy	1975
Wymox	Wyeth	U.S.	1978
Utimox	WL/PD	U.S.	1979
Agerpen	Cepa	Spain	—
A-Gram	Inava	France	—
Alfamox	Alfa	Italy	—
Alfida	Esteve	Spain	—
Alfoxil	Fako	Turkey	—
Am-73	Medici	Italy	—
Amocilline	Inpharzam	Belgium	—
Amoclen	Spofa	Czechoslovakia	—
Amodex	Robert & Carriere	France	—
Amo-Flamisan	Mazuelos	Spain	—
Amoksilin	Nobel	Turkey	—
Amoksina	Mustafa Nevzat	Turkey	—
Amolin	Takeda	Japan	—
Amorion	Orion	Finland	—
Amosin	Sanli	Turkey	—
Amox	Lusofarmaco	Spain	—
Amox	Prodes	Spain	—
Amoxamil	Lafi	Brazil	—
Amoxaren	Areu	Spain	—
Amoxi-Basileos	Basileos	Spain	—
Amoxibiotic	Aristochimica	Italy	—
Amoxicil	Dincel	Turkey	—
Amoxicillin	Toho	Japan	—
Amoxidal	Roemmers	Argentina	—
Amoxidin	Lagap	Switz.	—
Amoxi-Gobens	Normon	Spain	—
Amoxillin	Esseti	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
Amoximedical	Medical	Spain	–
Amoxipen	Gibipharma	Italy	–
Amoxipenil	Montpellier	Argentina	–
Amoxiroger	Roger	Spain	–
Amoxi-Tabs	Beecham	–	–
Amoxypen	Grunenthal	W. Germany	–
Amplimox	Ausonia	Italy	–
Amplimox	Iton	Italy	–
Ampy-Penyl	Proto	Switz.	–
Apitart	Isei	Japan	–
Ardine	Antibioticos	Spain	–
Aspenil	Chemil	Italy	–
Augmentin	Beecham	U.S.	–
Ax-1000	Durachemie	W. Germany	–
Axbiot	Galepharma Iberica	Spain	–
Becabil	Alfar	Spain	–
Benzoral	Biosintetica	Brazil	–
Bioxidona	Faes	Spain	–
Bristamox	Bristol	–	–
Cabermox	Caber	Italy	–
Chitacillin	Banyu	Japan	–
Cidanamox	Cidan	Spain	–
Clamox	Roussel-Diamant	Morocco	–
Clamoxyl	Wulfing	W. Germany	–
Clamoxyl	Beecham-Sevigne	France	–
Dacala	Guadalupe	Spain	–
Damoxicil	Elmu	Spain	–
Daxipen	Recofarma	Brazil	–
Delacillin	Sankyo	Japan	–
Demoksil	Deva	Turkey	–
Doksilin	Iltas	Turkey	–
Draximox	Novo	–	–
Efpenix	Toyo Jozo	Japan	–
Eupen	Uriach	Spain	–
Flemoxin	Gist-Brocades	–	–
Fullcilina	Sintyal	Argentina	–
Grinsil	Argentia	Argentina	–
Hiconcil	Allard	France	–
Himinomax	Kaken	Japan	–
Hosboral	Hosbon	Spain	–
Ibiamox	IBI	Italy	–
Imacillin	Astra	–	–
Infectomycin	Heyden	W. Germany	–
Isimoxin	ISI	Italy	–
Kapoxi	Kappa	Spain	–
Largopen	Bilim	Turkey	–
Majorpen	Cyanamid	U.S.	–
Megacillin	Mulda	Turkey	–
Metifarma	Novofarma	Spain	–
Morgenxil	Morgens	Spain	–
Moxacin	C.S.L.	Australia	–
Moxal	Roger Bellon	Italy	–
Moxalin	Mead-Johnson	U.S.	–
Moxilean	Organon	–	–
Moxipin	Gamir	Spain	–
Moxypen	Teva	Israel	–
Novamoxin	Novopharma	Canada	–

Trade Name	Manufacturer	Country	Year Introduced
Nuvosyl	Mepha	Switz.	–
Optium	Disprovent	Argentina	–
Ospanox	Biochemie	Austria	–
Pamocil	Lancet	Italy	–
Paradroxil	Bristol	–	–
Pasetocin	Kyowa	Japan	–
Penamox	Beecham	–	–
Penimox	Ibsa	Switz.	–
Piramox	Pharmax	Italy	–
Precopen	Fides	Spain	–
Primasin	Eczacibasi	Turkey	–
Raudopen	Alter	Spain	–
Raylina	Robert	Spain	–
Reloxyl	Biologia Marina	Spain	–
Remoxil	Kimya Evi	Turkey	–
Rivoxicillin	Rivopharm	Switz.	–
Robamox	Robins	U.S.	–
Sancixomal	Santos	Spain	–
Sawamezin	Sawai	Japan	–
Sigamopen	Siegfried	Switz.	–
Simplamox	ISF	Italy	–
Sinacilin	Galenika	Yugoslavia	–
Sintedix	Castillon	Spain	–
Sintoplus	Aesculapius	Italy	–
Sumox	Reid-Provident	U.S.	–
Superpeni	Efeyn	Spain	–
Tolodina	Estedi	Spain	–
Triamoxil	Squibb	U.S.	–
Trifamox	Bago	Argentina	–
Trimoksilin	Abdi Ibrahim	Turkey	–
Trimox	Squibb	U.S.	–
Unicillin	Tobishi	Japan	–
Uro-Clamoxyl	Beecham	–	–
Utimox	Parke Davis	–	–
Wassermox	Wassermann	Spain	–
Widecillin	Meiji	Japan	–
Zamocillin	Zambon	Italy	–
Zimox	Farmitalia Carlo Erba	Italy	–

Raw Materials

6-Aminopenicillanic Acid
Ethyl Chlorocarbonate
Sodium Bicarbonate
Hydrogen
O,N-Dibenzyloxycarbonyl-p-oxy-di-α-aminophenylacetic Acid

Manufacturing Process

Ethyl chlorocarbonate (2.2 ml) was added to an ice cold solution of O,N-dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetic acid (10 grams) and triethylamine (3.85 ml) in dry acetone (193 ml). The mixture was stirred at 0°C for 5 minutes during which triethylamine hydrochloride precipitated. The suspension was cooled to -30°C and stirred vigorously while adding as rapidly as possible an ice cold solution of 6-aminopenicillanic acid (5.85 grams) in 3% aqueous sodium bicarbonate (193 ml), the temperature of the mixture never being allowed to rise above 0°C. The resulting clear solution was stirred for 30 minutes at 0°C, and then for a further 30 minutes, without external cooling, and finally extracted with diethyl ether (3 x 200 ml) only the aqueous phase being retained.

This aqueous solution was brought to pH 2 by the addition of hydrochloric acid and the

6-(O,N-dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetamido)-penicillanic acid so liberated was extracted into diethyl ether (50 ml and 2 portions of 30 ml). The ether phase was washed with water (3 x 5 ml) and the water washings were discarded.

Finally, the penicillin was converted to the sodium salt by shaking the ether solution with sufficient 3% sodium bicarbonate to give a neutral aqueous phase, separating the latter and evaporating it at low pressure and temperature below 20°C. The product was finally dried over phosphorus pentoxide in vacuo to give sodium 6-(O,N-dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetamido)-penicillanate (9.2 grams).

A suspension of palladium on calcium carbonate (36 grams of 5%) in water (150 ml) was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure for 1 hour. A neutral solution of sodium 6-(O,N-dibenzyloxycarbonyl-p-oxy-dl-α-aminophenylacetamido)-penicillanate (9 grams) in water (100 ml) was then added and shaking in hydrogen was resumed for one hour. The suspension was then filtered and the collected catalyst was washed well with water without being allowed to suck dry between washings. The combined filtrate and washings were then brought to pH 6.5 with dilute hydrochloric acid and evaporated to dryness at reduced pressure and temperatures below 20°C. The product was finally dried over phosphorus pentoxide in vacuo to give a solid (5.4 grams) containing 6-(p-hydroxy-dl-α-aminophenylacetamido)-penicillanic acid.

References

Merck Index 600
Kleeman & Engel p. 48
PDR pp. 658, 673, 705, 993, 1315, 1606, 1769, 1997
OCDS Vol. 1 p. 414
DOT 19 (3) 169 (1983)
I.N. p. 79
REM p. 1193
Nayler, J.H.C. and Smith, H.; U.S. Patent 3,192,198; June 29, 1965

AMPHETAMINE PHOSPHATE

Therapeutic Function: Central stimulant

Chemical Name: 1-Phenyl-2-aminopropane monophosphate

Common Name: –

Structural Formula: $C_6H_5CH_2CH(NH_2)CH_3 \cdot H_3PO_4$

Chemical Abstracts Registry No.: 139-10-6

Trade Name	Manufacturer	Country	Year Introduced
Raphetamine	Strasenburgh	U.S.	1950
Amphate	Storck	U.S.	–
Leptamine	Bowman	U.S.	–
Monophos	Durst	U.S.	–
Profetamine	Clark & Clark	U.S.	–

Raw Materials

Phenyl Nitropropylene
Phosphoric Acid

Chemical Abstracts Registry No.: 1402-82-0 (Base)

Manufacturing Process

1 mol of phenyl-nitropropylene, $C_6H_5CH{=}C(CH_3)NO_2$, is dissolved with a solvent prepared by mixing one liter of ethanol with one-half liter of acetic acid and one-half liter of 12 N sulfuric acid. The resultant solution is placed in the cathode compartment of a divided electrolytic cell containing a metallic cathode of mercury, copper, or other metal of similar nature. Current is passed, using a current density of ~0.2 amp/cm^2 of cathode surface. The temperature is kept at about 40°C during the electrolysis which is continued until at least eight Faradays of electricity have been passed.

When the reduction is completed, the 1-phenyl-2-aminopropane may be separated from the solution. A convenient way of doing this is by removing the ethanol and ethyl acetate present by evaporation and then making the residual solution strongly alkaline by addition of caustic alkali. The basic layer thus formed is separated from the aqueous solution and contains the desired 1-phenyl-2-aminopropane.

135 g (1 mol) of amphetamine (1-phenyl-2-aminopropane) were stirred into 300 cc of acetone in a stainless-steel vessel. To the resultant solution there were slowly added under constant agitation 115.3 g of 85% phosphoric acid (containing 1 mol of H_3PO_4), care being taken to avoid any sudden rise in temperature or local overheating due to the considerable amount of heat that is evolved. During the addition of the phosphoric acid a fine, white, flocculent precipitate appears which becomes more and more dense and abundant, as the quantity of added acid increases.

When the entire quantity of the phosphoric acid has thus been added, agitation of the mixture is continued for about a half-hour or more to insure complete conversion. The precipitate is then allowed to settle, the supernatant liquid is drawn off, and the residue is filtered. The precipitate thus separated may, if desired, be washed with acetone and is then dried by evaporation to constant weight. It forms a fine, white, impalpable powder consisting of pure monobasic amphetamine phosphate.

References

Merck Index 607
I.N. p. 80
Alles, G.A.; U.S. Patent 1,879,003; September 27, 1932 (amphetamine base mfg.)
Goggin, T.C.; U.S. Patent 2,507,468; May 9, 1950; assigned to Clark & Clark Co. (amphetamine conversion to phosphate)

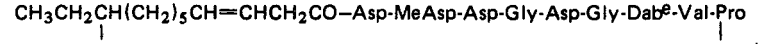
AMPHOMYCIN CALCIUM

Therapeutic Function: Antibiotic

Chemical Name: Amphomycin calcium

Common Name: Glumamicin

Structural Formula:



Dab^e = D-erythro-α,β-diaminobutyric acid
Dab^t = L-threo-α,β-diaminobutyric acid
Pip = D-pipecolic acid

(base)

Trade Name	Manufacturer	Country	Year Introduced
Amphocortrin CR	Warner-Lambert	U.S.	1963

Raw Materials

Amphomycin
Calcium Hydroxide

Manufacturing Process

The process for producing amphomycin comprises cultivating a strain of *Streptomyces canus* in an aqueous, nutrient-containing carbohydrate solution under submerged aerobic conditions until substantial antibacterial activity is imparted to the solution and then recovering the so-produced amphomycin from the fermentation broth.

The process of decolorizing solutions of amphomycin then involves treatment with activated charcoal, followed by the steps of (1) extracting the antibiotic into a water-immiscible organic solvent under strongly acid conditions or precipitating the amphomycin from aqueous solution by adjusting the pH to a point within the range of pH 3.0 to 4.0, (2) removing impurities from strongly acid, aqueous solution of amphomycin by extraction of the impurities with methyl isobutyl ketone and amyl acetate, (3) extracting the amphomycin from a strongly acid solution in butanol by the use of water having a pH higher than 4, (4) extracting the amphomycin from solution in water-immiscible organic solvent into water whose pH is greater than 6.0, (5) precipitating amphomycin from solution by formation of insoluble derivatives of the basic function, and (6) precipitating amphomycin from solution by formation of insoluble derivates of the acidic function.

The amphomycin is then converted to the calcium salt with calcium hydroxide.

References

Merck Index 609
Heinemann, B., Cooper, I.R. and Kaplan, M.A.; U.S. Patent 3,126,317; March 24, 1964; assigned to Bristol-Myers Co.

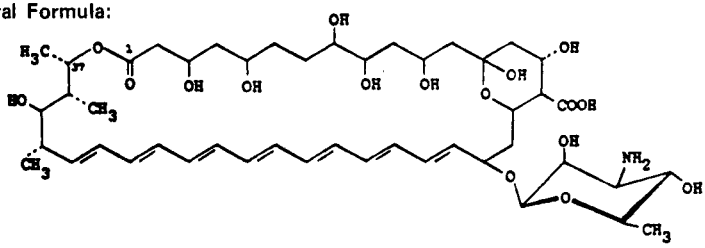
AMPHOTERICIN B

Therapeutic Function: Antifungal

Chemical Name: [1R-(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E,29E,31E,33R*,35S*,36R*,37S*)]-33-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 1397-89-3

Trade Name	Manufacturer	Country	Year Introduced
Fungizone	Squibb	U.S.	1958
Ampho-Moronal	Heyden	W. Germany	–
Fungizone	Squibb	France	1969
Amphocycline	Squibb	France	–
Amphozone	Squibb	–	–
Fungilin	Squibb	U.K.	–
Fungilin	Squibb	Italy	–
Fungizone	Squibb-Sankyo	Japan	–
Mysteclin	Heyden	W. Germany	–

Raw Materials

Carbohydrates
Streptomyces nodosus

Manufacturing Process

The process for producing amphotericin comprises cultivating a strain of *Streptomyces nodosus* in an aqueous nutrient medium comprising an assimilable, fermentable carbohydrate and an assimilable organic nitrogen source, under submerged aerobic conditions, until substantial antifungal activity is imparted to the medium and recovering amphotericin from the medium.

References

Merck Index 611
Kleeman & Engel p. 50
PDR pp. 1743, 1752
DOT 7 (5) 192 (1971)
I.N. p. 81
REM p. 1226
Dutcher, J.D., Gold, W., Pagano, J.F. and Vandeputte, J.; U.S. Patent 2,908,611; October 13, 1959; assigned to Olin Mathieson Chemical Corporation

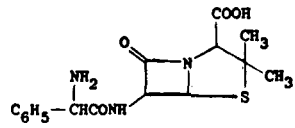
AMPICILLIN

Therapeutic Function: Antibacterial

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

Common Name: D-α-aminobenzylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 69-53-4

Trade Name	Manufacturer	Country	Year Introduced
Binotal	Bayer	W. Germany	1962

Trade Name	Manufacturer	Country	Year Introduced
Penicline	Delagrange	France	1963
Penbritin	Ayerst	U.S.	1963
Penbritin	Beecham	U.K.	1963
Omnipen	Wyeth	U.S.	1966
Ampisint	Proter	Italy	1969
Acucillin	Fuji	Japan	–
Adobacillin	Tobishi	Japan	–
Albipen	Gist Brocades	–	–
Alfasilin	Fako	Turkey	–
Almopen	Gist Brocades	–	–
Alpen	Lederle	U.S.	–
Amblosen	Hoechst	W. Germany	–
Amcill	Parke-Davis	U.S.	–
Amfipen	Gist Brocades	U.K.	–
Amfipen	Schering	W. Germany	–
Amipenix	Toyo Jozo	Japan	–
Ampen	Medosan	Italy	–
Ampen	ICN	Canada	–
Ampensaar	Chephasaar	W. Germany	–
Ampibeta	Violani-Farmavigor	Italy	–
Ampibiotic	Ottolenghi	Italy	–
Ampicil	Ausonia	Italy	–
Ampicillina Pharmax	Pharmax	Italy	–
Ampicillina Pierrel	Pierrel	Italy	–
Ampicina	Sigma Tau	Italy	–
Ampicyn	Protea	Australia	–
Ampifen	Intersint	Italy	–
Ampikel	Dreikehl	Spain	–
Ampilan	Ibern	Italy	–
Ampiland	Landerlan	Spain	–
Ampilisa	Lisapharma	Italy	–
Ampilux	Tubi Lux Pharma	Italy	–
Ampimed	Aristochimica	Italy	–
Ampinebiot	Bertran Hathor	Spain	–
Ampinova	Cheminova Espanola	Spain	–
Ampinoxi	Therapia	Spain	–
Ampiopen	Ibern	Italy	–
Ampi-Plena Simple	Pradel	Spain	–
Ampisil	Dif-Dogu	Turkey	–
Ampisina	Mustafa Nevzat	Turkey	–
Ampi-Tablinen	Sanorania	W. Germany	–
Ampitex	Neopharmed	Italy	–
Ampivax	Ripari-Gero	Italy	–
Ampixyl	Pharma-Plus	Switz.	–
Amplenil	Orma	Italy	–
Amplibios	Panther-Osfa Chemie	Italy	–
Amplicid	Cifa	Italy	–
Amplipen	Labif	Italy	–
Amplipenyl	ISF	Italy	–
Ampliscocil	I.C.I.	Italy	–
Amplisom	Isom	Italy	–
Amplital	Farmitalia Carlo Erba	Italy	–
Amplizer	O.F.F.	Italy	–
Anhypen	Gist Brocades	–	–
Anidropen	Wyeth	Italy	–
Anticyl	San Carlo	Italy	–
A-Pen	Orion	Finland	–

Trade Name	Manufacturer	Country	Year Introduced
Argocillina	Beta	Italy	–
Austrapen	CSI	Australia	–
Benusel	ICN	–	–
Bio-Ampi	Donatello	Italy	–
Biocellina	Magis	Italy	–
Bionacillin	Takata	Japan	–
Bonapicillin	Taiyo	Japan	–
Britapen Oral	Federico Bonet	Spain	–
Britcin	DDSA	U.K.	–
Bropicilina	Byk Golden	–	–
Cilleral	Bristol-Banyu	Japan	–
Citicil	C.T.	Italy	–
Combipenix	Toyo Jozo	Japan	–
Copharcilin	Cophar	Switz.	–
Deripen	Schering	W. Germany	–
Doktacillin	Astra	–	–
Domicillin	Dainippon	Japan	–
Drisilin	Drifen	Turkey	–
Espectrosira	Clariana	Spain	–
Eurocillin	Borromeo	Italy	–
Farmampil	Gazzini	Italy	–
Fidesbiotic	Fides	Spain	–
Fortapen	Continental Pharma	Belgium	–
Geycillina	Geymonat	Italy	–
Gramcillina	Caber	Italy	–
Grampenil	Argentina	Argentina	–
Guicitrina	Perga	Spain	–
Hostes Pedriatico	Lando	Argentina	–
Ikapen	Ikapharm	Israel	–
Isocillin	Kanto	Japan	–
Iwacillin	Iwaki	Japan	–
Lampocillina Orale	Sidus	Italy	–
Lifeampil	Lifepharma	Spain	–
Marisilan	Wakamoto	Japan	–
Makrosilin	Atabay	Turkey	–
Maxicilina	Antibioticos	Spain	–
Napacil	Montefarmaco	Italy	–
NC-Cillin	Nippon Chemiphar	Japan	–
Negopen	Deva	Turkey	–
Nuvapen	Cepa	Spain	–
Orocilin	Isa	Brazil	–
Overcillina	Lepetit	Italy	–
Overcillina	Archifar	Italy	–
Pen Ampil	Nuovo. Const. Sanit. Naz.	Italy	–
Penbrock	Beecham	–	–
Penibrin	Teva	Israel	–
Penimic	SS Pharm.	Japan	–
Peninovel	Larma	Spain	–
Penisint B.G.	Boniscontro	Italy	–
Penoral	Nobel	Turkey	–
Penorsin	Wassermann	Spain	–
Pentrex	Banyu	Japan	–
Pentrexyl	Galenika	Yugoslavia	–
Pharcillin	Toyo Pharm	Japan	–
Platocillina	Crosara	Italy	–
Plumericin	Torlan	Spain	–

Trade Name	Manufacturer	Country	Year Introduced
Policilin	Bristol	–	–
Polycillin	Bristol	U.S.	–
Principen	Squibb	U.S.	–
Quimetam	Quimicos Unidos	Spain	–
Radiocillina	Radium Pharma	Italy	–
Recenacillin	Maruko	Japan	–
Resan	Alacan	Spain	–
Rivocillin	Rivopharm	Switz.	–
Saicil	Libra	Italy	–
Sentapent	Kimya Evi	Turkey	–
Sernabiotic	Libra	Italy	–
Sesquicillina	Ita	Italy	–
Sintopenyl	Aesculapius	Italy	–
SK-Ampicillin	SK&F	U.S.	–
Togram	Morgens	Spain	–
Tokiocillin	Isei	Japan	–
Totacillin	Beecham	Japan	–
Totaclox	Beecham	Japan	–
Totalciclina	Benvegna	Italy	–
Totapen	Bristol	France	–
Trafarbiot	Novopharma	Spain	–
Ultrabion	Lifasa	Spain	–
Vastacyn	Ankerfarm	Italy	–
Vexampil	Ifi	Italy	–
Viccillin	Meiji	Japan	–

Raw Materials

α-Aminophenylacetic Acid
Ethyl Chlorocarbonate
6-Aminopenicillanic Acid
Benzyl Chlorocarbonate
Hydrogen

Manufacturing Process

α-Carbobenzyloxyaminophenylacetic acid (0.1 mol), which is obtained by the reaction of equivalent quantities of α-aminophenylacetic acid and benzyl chlorocarbonate in aqueous sodium hydroxide, dissolved in dry acetone is stirred and cooled to approximately -5°C. To this there is added dropwise with continued cooling and stirring a solution of ethyl chlorocarbonate (0.1 mol). After approximately 10 minutes, the acylating mixture is cooled to about -5°C and then is slowly added to a stirred ice-cold mixture of 6-aminopenicillanic acid (0.1 mol), 3% sodium bicarbonate solution (0.1 mol) and acetone. This reaction mixture is allowed to attain room temperature, stirred for an additional thirty minutes at this temperature and then is extracted with ether.

The extracted aqueous solution is covered with butanol and the pH adjusted to 2 by the addition of N HCl. The acidified aqueous phase is extracted with butanol, the pH of the aqueous phase being adjusted to pH 2 each time. The combined butanol solutions which contain the free acid, α-carbobenzyloxyaminobenzylpenicillin, are washed with water, and are then shaken with water to which sufficient 3% sodium bicarbonate has been added to bring the aqueous phase to pH 7. The process of washing and shaking is repeated with fresh water and bicarbonate solution. The combined aqueous solutions are washed with ether and then are evaporated under reduced pressure and low temperature. The product, the sodium salt of α-carbobenzyloxyaminobenzylpenicillin, is obtained as a yellow solid in a yield of 65%.

A suspension of palladium on barium carbonate (3.7 grams of 30%) in water (20 ml) is shaken in an atmosphere of hydrogen at room temperature. The catalyst is then filtered and washed well with water, care being taken that it does not become dry. A solution of the

sodium salt of α-carbobenzyloxyaminobenzylpenicillin (4 grams) in water (20 ml) is added to the pretreated catalyst and the suspension is shaken in an atmosphere of hydrogen at room temperature and pressure for one hour. The catalyst is then filtered off, washed well with water, and the combined filtrate and washings adjusted to pH 7 with N hydrochloric acid. The resulting solution is evaporated in vacuo at a temperature below 20°C to give α-aminobenzylpenicillin (2.4 grams, 74% yield), which is assayed at approximately 48% pure by the manometric method.

References

Merck Index 612
Kleeman & Engel p. 50
PDR pp. 673, 703, 1314, 1722, 1964
OCDS Vol. 1 p. 413; Vol. 2 p. 437
I.N. p. 81
REM p. 1194
Doyle, F.P., Nayler, J.H.C., and Smith, H.; U.S. Patent 2,985,648; May 23, 1961
Kaufmann, W. and Bauer, K.; U.S. Patent 3,079,307; Feb. 26, 1963; assigned to Farbenfabriken Bayer AG, Germany
Johnson, D.A. and Wolfe, S.; U.S. Patnet 3,140,282; July 7, 1964; assigned to Bristol-Myers Company
Grant, N.H. and Alburn, H.E.; U.S. Patent 3,144,445; August 11, 1964; assigned to American Home Products Corporation

AMPICILLIN TRIHYDRATE

Therapeutic Function: Antibacterial

Chemical Name: See Ampicillin

Common Name: —

Structural Formula: See Ampicillin

Chemical Abstracts Registry No.: 7177-48-2

Trade Name	Manufacturer	Country	Year Introduced
Polycillin	Bristol	U.S.	1963
Principen	Squibb	U.S.	1967
Amcill	Parke Davis	U.S.	1968
Alpen	Lederle	U.S.	1969
Totacillin	Beecham	U.S.	1970
Pensyn	Upjohn	U.S.	1972
Ro-Ampen	Rowell	U.S.	1972
Pen A	Pfizer	U.S.	1972
Trimox	Squibb	U.S.	1978
AB-PC	Tojo Jozo	Japan	—
Acillin	ICN	—	—
Amblosin	Hoechst	—	—
Amcap	Circle	U.S.	—
Amperil	Geneva Drugs	U.S.	—
Ampexin	Therapex	Canada	—
Ampical	*Uva*	*France*	—
Ampichelle	Rachelle	U.S.	—

Trade Name	Manufacturer	Country	Year Introduced
Ampicil	Jeba	Spain	–
Ampiciman	Liberman	Spain	–
Ampi-Co	Coastal	U.S.	–
Ampifar	Benedetti	Italy	–
Ampikel	Dreikehl	Spain	–
Ampilag	Lagap	Switz.	–
Ampileta	Letap	Switz.	–
Ampi-Oral	Biologia Marina	Spain	–
Ampiorus	Horus	Spain	–
Ampiscel	Rachelle	U.S.	–
Ampixyl	Pharma-Plus	Switz.	–
Ampi-Zoja	Zoja	Italy	–
Amplin	Winston	U.S.	–
Arcocillin	ICN	–	–
Benusel	ICN	–	–
Binotal	Bayer	–	–
Cetampin	CTA Pharma	Switz.	–
Cetampin	Scarium	Switz.	–
Cimexillin	Cimex	Switz.	–
Cymbi	Dolorgiet	W. Germany	–
Citicil	C.T.	Italy	–
D-Amp	Dunhall	U.S.	–
D-Cillin	Dunhall	U.S.	–
Delcillin	Marlop	U.S.	–
Divercillin	Ascher	U.S.	–
Dumopen	Dumex	Denmark	–
Dur Ampicillin	Durachemie	W. Germany	–
Espimin-Cilin	Spyfarma	Spain	–
Fuerpen	Hermes	Spain	–
Gobemicina Simple	Normon	Spain	–
Helvecillin	Helvepharm	Switz.	–
Lifeampil	Lifepharma	Spain	–
Morepen	Morejon	Spain	–
Novoexpectro	Aldon	Spain	–
Penbristol	Bristol-Myers	Austria	–
Penimaster	Liade	Spain	–
Peninovel	Larma	Spain	–
Pentraxyl	Bristol	–	–
Pentrexyl Oral	Antibioticos	Spain	–
Pentricine	Ibsa	Switz.	–
Poenbiotico	Poen	Argentina	–
Prestacilina	Pental	Spain	–
Q I Damp	Mallinckrodt	U.S.	–
Rosampline	Rosa-Phytopharma	France	–
Servicillin	Servipharm	Switz.	–
Standacillin	Biochemie	Austria	–
Sumipanto Oral	Asia	Spain	–
Texcillin	First Texas	U.S.	–
Trafarbior	Novopharma	Spain	–
Trafacilina	Bago	Argentina	–
Vampen	Vangard	U.S.	–
Vidopen	Berk	U.K.	–

Raw Materials

Ampicillin Beta Naphthalene Sulfonate
Secondary Amines

Manufacturing Process

The known methods for the preparation of D-(-)-α-aminobenzylpenicillin by the acylation of 6-aminopenicillanic acid result in the preparation of aqueous mixtures which contain, in addition to the desired penicillin, unreacted 6-aminopenicillanic acid, hydrolyzed acylating agent, and products of side reactions such as the products of the acylating agent reacted with itself and/or with the desired penicillin, as well as other impurities.

The D-(-)-α-aminobenzylpenicillin may then be recovered from the aqueous reaction mixture by concentration to small volume and recovering the product by filtration. However, due to the fact that anhydrous D-(-)-α-aminobenzylpenicillin is soluble in water to the extent of about 20-25 mg/ml at 20°-25°C, it is very difficult to recover the product in high yields. Furthermore, the recovered D-(-)-α-aminobenzylpenicillin may be obtained in the form of a monohydrate. The monohydrates (as well as the dihydrates) of D-(-)-α-aminobenzylpenicillin possess poor biological stability.

The trihydrate which is obtained in high yields, is relatively insoluble in water, possesses high biological stability and can be obtained by contacting, at a temperature not above 60°C, an acid addition salt of D-(-)-α-aminobenzylpenicillin with an amine in a water-immiscible solvent containing at least 3 mols of water per mol of such penicillin.

The following is an example of the conduct of such a process. To a vigorously agitated mixture of 100 ml of methyl isobutyl ketone there are added at 25° to 30°C 15 ml of water and 10 ml of a mixture of secondary amines.

To this mixture there is then added slowly over a period of 30 minutes 10 grams of D-(-)-α-aminobenzylpenicillin beta-naphthalene sulfonate. The mixture is agitated for 3 hours at 25°-30°C. The product, D-(-)-α-aminobenzylpenicillin trihydrate precipitates and is collected by filtration. The filter cake of the product is washed several times with methyl isobutyl ketone and is dried at 40°C. The product is obtained in about a 90% yield and has a potency of 865 mcg/mg. It is determined by Karl Fischer analysis to have a moisture content of 13.4% by weight.

References

Merck Index 612
Kleeman & Engel p. 81
PDR pp. 993, 1606, 1758
I.N. p. 50
Johnson, D.A. and Hardcastle, G.A., Jr.; U.S. Patent 3,157,640; November 17, 1964; assigned to Bristol-Myers Company

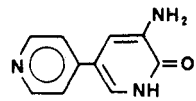
AMRINONE

Therapeutic Function: Cardiotonic

Chemical Name: 3-Amino-5-(4-pyridinyl)-2(1H)-pyridinone

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 60719-84-8

Trade Name	Manufacturer	Country	Year Introduced
Inocor	Sterling Winthrop	Philippines	1982
Inocor	Sterling Winthrop	Mexico	1983
Wincoram	–	–	–

Raw Materials

3-Nitro-5-(4-pyridinyl)-2(1H)-pyridinone
Hydrogen

Manufacturing Process

A mixture containing 10 g of 3-nitro-5-(4-pyridinyl)-2(1H)-pyridinone, 200 ml of dimethylformamide and 1.5 g of 10% palladium-on-charcoal was hydrogenated under pressure (50 psi) at room temperature until the uptake of hydrogen ceased (about 30 minutes). The reaction mixture was filtered through infusorial earth and the filtrate was heated in vacuo to remove the solvent. The residual material was crystallized from dimethylformamide, washed successively with ethanol and ether, and dried in a vacuum oven at 80°C for 8 hours to yield 6 g of 3-amino-5-(4-pyridinyl)-2(1H)-pyridinone, melting point 294° to 297°C with decomposition.

References

Merck Index 616
DFU 4 (4) 245 (1979)
PDR p. 1909
OCDS Vol. 3 p. 147
DOT 18 (10) 547 (1982) & 19 (10) 581 (1983)
I.N. p. 85
Lesher, G.Y. and Opalka, C.J.; U.S. Patent 4,004,012; January 18, 1977; assigned to Sterling Drug Inc.
Lesher, G.Y. and Opalka, C.J.; U.S. Patent 4,107,315; August 15, 1978; assigned to Sterling Drug Inc.

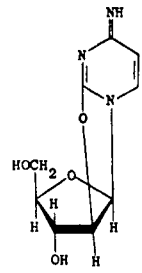
ANCITABINE HYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: 2,3,3a,9a-Tetrahydro-3-hydroxy-6-imino-6H-furo[2',3';4,5]oxazolo[3,2-a]-pyrimidine-2-methanol

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 10212-25-6; 31698-14-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cyclo-C	Kohjin	Japan	1975

Raw Materials

Uridine
Trityl Chloride
Imidazole
Thiophosgene
Hydrogen Sulfide
Acetic Acid
Acetic Anhydride
Phosphorus Pentasulfide
Ammonia
Bromine
Hydrogen Chloride

Manufacturing Process

A series of reaction steps may be employed in which: (1) Uridine is reacted with trityl chloride to give 5'-o-trityluridine; (2) Imidazole is reacted with thiophosgene and that product reacted with the 5'-o-trityluridine to give 2,2'-anhydro-1-(5'-o-trityl-β-D-arabinofuranosyl)uracil; (3) The preceding uracil product is converted to the thiouracil using hydrogen sulfide; (4) The trityl group is removed by treatment with 80% acetic acid; (5) A triacetylated product is obtained using acetic anhydride; (6) A dithiouracil is prepared from the uracil intermediate using phosphate pentasulfide.

Preparation of 1-(β-D-arabinofuranosyl)-2-thiocytosine: A solution of 2.0 g of 1-(2',3',5'-O-triacetyl-β-D-arabinofuranosyl)-2,4-dithiouracil in 100 ml of methanol is saturated with anhydrous ammonia at 0°C. The mixture, in a glass liner, is heated in a pressure bomb at 100°C for three hours. The reaction mixture is concentrated to a gum in vacuo, and most of the by-product acetamide is removed by sublimation at 60°C/0.1 mm. The residue is chromatographed on 100 g of silica gel. Elution of the column with methylene chloride-methanol mixtures with methanol concentrations of 2–25% gives fractions containing acetamide and a series of brown gums. The desired product is eluted with 30% methanol-methylene chloride to give a total yield of 0.386 g (30%), MP 175°–180°C (dec.). Recrystallization from methanol-isopropanol furnishes an analytical sample, MP 180°–182°C (dec.).

To a solution of 80 mg of 1-(β-D-arabinofuranosyl)-2-thiocytosine in 12 ml of water is added dropwise 3 ml of a 1 M bromine solution in carbon tetrachloride. At this point the color of the bromine persists for about 2–3 minutes after each addition. The unreacted bromine is blown off with a stream of nitrogen, and the reaction mixture is concentrated to a syrup in vacuo using a bath temperature less than 50°C. The residue is evaporated three times with 10 ml portions of ethanol, whereupon it crystallizes. The product is triturated with cold ethanol and with ether to obtain 17 mg of 2,2'-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrobromide, MP 240°C (dec.).

Treatment of the hydrobromide with a slight excess of ethanolic ammonia yields the base which may then be converted to the hydrochloride.

References

Merck Index 654
Kleeman & Engel p. 53
DOT 12 (8) 304 (1976)
I.N. p. 87
Shen, T.Y. and Ruyle, W.V.; U.S. Patent 3,463,850; August 26, 1969; assigned to Merck & Co., Inc.

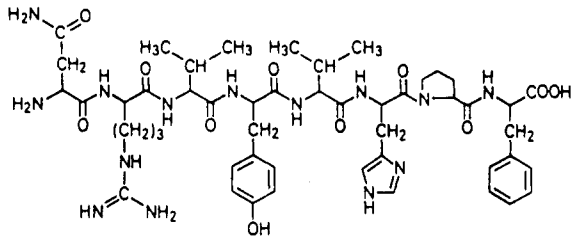
ANGIOTENSIN AMIDE

Therapeutic Function: Vasoconstrictor

Chemical Name: L-asparaginyl-L-arginyl-L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-protyl-L-phenylalanine

Common Name: –

Structural Formula:



H–Asn-Arg-Val-Tyr-Val-His-Pro-Phe–OH

Chemical Abstracts Registry No.: 53-73-6

Trade Name	Manufacturer	Country	Year Introduced
Hypertensin	Ciba	W. Germany	1961
Hypertensin	Ciba	U.S.	1962

Raw Materials

L-Asparaginyl-L-arginyl-L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester trihydrochloride
Sodium hydroxide

Manufacturing Process

48 mg (0.042 mmol) of L-asparaginyl-L-arginyl-L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester trihydrochloride are suspended in 0.5 ml of methanol, and treated gradually in the course of one hour with 0.3 ml of N-caustic soda solution (about 7 equivalents) so that the pH value of the solution is maintained between 10.5 and 11.5. After a further 30 minutes the solution is freed from methanol under vacuum at room temperature, adjusted with 1 N-acetic acid to pH 7.4 and lyophilized. The residual mixture of free peptide and inorganic salts (79 mg) is fractionated by countercurrent distribution in the system butanol/0.1 N-ammonium hydroxide. The pure octapeptide is obtained as a colorless powder which is soluble in water and methanol, more sparingly soluble in ethanol, and insoluble in acetone.

References

Merck Index 674
Kleeman & Engel p. 55
I.N. p. 89
Schwyzer, R., Iselin, B., Kappeler, H., Ritter, W. and Riuiker, B.; U.S. Patent 2,978,444; April 4, 1961; assigned to Ciba Pharmaceutical Products, Inc.

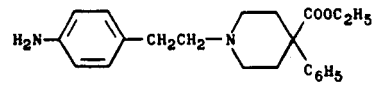
ANILERIDINE DIHYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: 1-[2-(4-aminophenyl)ethyl]-4-phenyl-4-piperidinecarboxylic acid ethyl ester dihydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 126-12-5; 144-14-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Leritine HCl	Merck Sharpe & Dohme	U.S.	1958
Apodol Tabs	Squibb	U.S.	1965
Leritine	Merck-Frosst	Canada	—

Raw Materials

β-(p-Aminophenyl)ethyl Chloride
4-Phenyl-4-carbethoxy Piperidine Carbonate
Sodium Carbonate
Hydrogen Chloride

Manufacturing Process

A mixture of 7.8 grams (0.05 mol) of β-(p-aminophenyl)ethyl chloride hydrochloride, 12.5 grams (0.025 mol) of 4-phenyl-4-carboethoxypiperidine carbonate, 10.5 grams (0.125 mol) sodium bicarbonate, and 100 cc of anhydrous ethanol are mixed, stirred and heated under reflux for a period of approximately 40 hours and then concentrated in vacuo to dryness. The residual material is triturated with 50 cc of water, decanted, washed by decantation with an additional 50 cc of water, and then dried in vacuo to give N-[β-(p-aminophenyl)-ethyl] -4-phenyl-4-carboethoxypiperidine.

The N-[β-(p-aminophenyl)ethyl]-4-phenyl-4-carboethoxypiperidine is dissolved in 50 cc of hot anhydrous ethanol, an excess (about 20 cc) of 20% alcoholic hydrochloric acid solution is added; upon scratching the side of the container crystals form. One hundred cubic centimeters of ether are then added to the mixture, the ethereal mixture is cooled, and the crystalline material which precipitates is recovered by filtration, washed with ether, and dried to give 12.7 grams of N-[β-(p-aminophenyl)ethyl] -4-phenyl-4-carboethoxypiperidine dihydrochloride which can be further purified by recrystallization from ethanol or methanol to give substantially pure material; MP 275°-277°C.

References

Merck Index 680
Kleeman & Engel p. 56
OCDS Vol. 1 p. 300 (1977)
I.N. p. 90
Weijlard, J. and Pfister, K., III; U.S. Patent 2,966,490; December 27, 1960; assigned to Merck & Co., Inc.

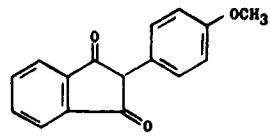
ANISINDIONE

Therapeutic Function: Anticoagulant

Chemical Name: 2-(4-methoxyphenyl)-1H-indene-1,3(2H)-dione

Common Name: Anisindandione

Structural Formula:



Chemical Abstracts Registry No.: 117-37-3

Trade Name	Manufacturer	Country	Year Introduced
Miradon	Schering	U.S.	1960
Unidone	Unilabo	France	1964
Unidone	Centrane	France	–

Raw Materials

p-Methoxybenzaldehyde
Sodium Ethoxide
Phthalide

Manufacturing Process

To a hot solution of 20.6 g of sodium in 400 ml of absolute ethanol, there is added a solution of 110 g of phthalide and 110 g of p-methoxybenzaldehyde. A vigorous reaction ensues and one-half of the alcohol is distilled off over a two hour period. Ice and water are added to the red solution and the diluted solution is acidified with hydrochloric acid. The resulting gum solidifies and the aqueous phase is removed by decantation. The crude solid is recrystallized twice from two liters of ethanol yielding 2-(p-methoxyphenyl)-1,3-indandione as pale yellow crystals, MP 155°-156°C.

References

Merck Index 690
Kleeman & Engel p. 57
OCDS Vol. 1 p. 147 (1977)
I.N. p. 90
REM p. 828
Sperber, N.; U.S. Patent 2,899,358; August 11, 1959; assigned to Schering Corporation

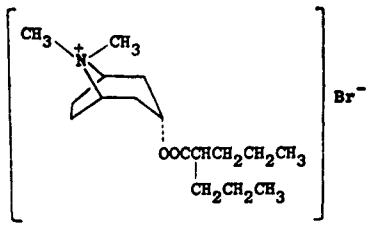
ANISOTROPINE METHYLBROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: endo-8,8-dimethyl-3-[(1-oxo-2-propylpentyl)oxy]-8-azoniabicyclo[3.2.1]-octane bromide

Common Name: Octatropine methyl bromide

Structural Formula:



Chemical Abstracts Registry No.: 80-50-2

Trade Name	Manufacturer	Country	Year Introduced
Valpin	Endo (Du Pont)	U.S.	1963
Valpinax	Crinos	Italy	1966
Valpin	Lacer	Spain	—
Valpin	Sankyo	Japan	—

Raw Materials

Tropine
Di-n-Propyl Acetyl Chloride
Methyl Bromide

Manufacturing Process

Preparation of Di-n-Propyl Acetyl Tropine Hydrochloride: Tropine (11.12 grams) was dissolved in 100 ml of anhydrous pyridine and to this solution was added 15.64 grams of di-n-propyl acetyl chloride. The mixture was refluxed for 6 hours. This solution was then cooled and the pyridine removed in vacuo. The residue was dissolved in chloroform. The chloroform solution was washed with 10% hydrochloric acid to remove the residual trace of pyridine. The hydrochloride of the product ester is soluble in chloroform and is not extracted from chloroform by hydrochloric acid. This is an unexpected property.

The chloroform solution of the hydrochloride was dried over anhydrous calcium sulfate, and evaporated to dryness, leaving a semisolid residue of product ester hydrochloride. This was recrystallized from chloroform-hexane mixture, MP 186°C.

Preparation of the Methyl Bromide: To the acetone solution of the free base was added an acetone solution, containing an excess of methyl bromide. Within a few minutes the methobromide started to crystallize. The mixture was allowed to stand for several hours. The crystallized solid was filtered, and additional product was obtained by evaporation of the filtrate. The yield was nearly quantitative. After recrystallization from acetone, the product melted at 329°C.

References

Merck Index 693
Kleeman & Engel p. 655
PDR p. 865
I.N. p. 699
REM p. 913
Weiner, N. and Gordon, S.M.; U.S. Patent 2,962,499; November 29, 1960; assigned to Endo Laboratories, Inc.

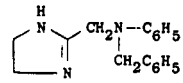
ANTAZOLINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: 4,5-Dihydro-N-phenyl-N-(phenylmethyl)-1H-imidazole-2-methanamine

Common Name: Imidamine

Structural Formula:



(base)

Chemical Abstracts Registry No.: 2508-72-7; 91-75-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Antistine HCl	Ciba	U.S.	1948
Antistine	Ciba Geigy	France	1948
Antistine	Ciba	W. Germany	–
Antasten	Ciba	–	–
Arithmin	Lannett	U.S.	–
Azalone	Smith, Miller & Patch	U.S.	–
Histotab	Boots	U.K.	–
Phenazoline	Polfa	Poland	–

Raw Materials

2-Chloromethylimidazoline HCl
N-Benzylaniline
Hydrogen Chloride

Manufacturing Process

15.4 parts of 2-chloromethylimidazoline-hydrochloride, 45.8 parts of N-benzylaniline and 150 parts of alcohol are heated in an oil bath at 100°to 110°C. After distilling off the alcohol, the reaction mass is maintained at this temperature for a further 3 hours and then triturated with water and 10 parts of sodium bicarbonate. The unconsumed benzylaniline is extracted with ether and the aqueous solution neutralized with dilute hydrochloric acid. By evaporating this solution and extracting the residue with alcohol there is obtained 2-(N-phenyl-N-benzyl-aminomethyl)-imidazoline-hydrochloride in the form of colorless crystals of melting point 227° to 229°C.

References

Merck Index 701
Kleeman & Engel p. 57
OCDS Vol. 1 p. 242 (1977)
I.N. p. 91
Miescher, K. and Klarer, W.; U.S. Patent 2,449,241; September 14, 1948; assigned to Ciba Pharmaceutical Products, Inc.

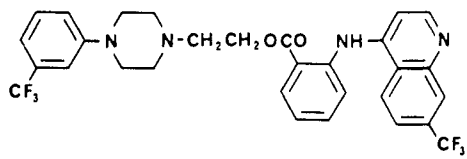
ANTRAFENINE

Therapeutic Function: Analgesic

Chemical Name: 2-(4'-m-Trifluoromethylphenyl-piperazino)-ethyl 2-(7'-trifluoromethyl-4'-quinolyl-amino)-benzoate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 55300-29-3

Trade Name	Manufacturer	Country	Year Introduced
Stakane	Dausse	France	1977

Raw Materials

Allyl 2-(7'-Trifluoromethyl-4'-quinolinyl-amino)benzoate
2-(4'-m-Trifluoromethylphenyl-piperazino)ethanol
Sodium

Manufacturing Process

A mixture of 18.65 g (0.05 mol) of allyl 2-(7'-trifluoromethyl-4'-quinolylamino)-benzoate, 16.2 g (0.059 mol) of 2-(4'-m-trifluoromethylphenyl-piperazino)-ethanol, 150 ml of anhydrous toluene and 0.03 g of sodium is heated under reflux for 2½ hours, while the allyl alcohol formed during the reaction is slowly removed by distillation. A slight amount of insoluble matter is filtered off and the toluene is evaporated from the filtrate. The residue is dissolved in a mixture of methylene chloride and acetone (8:2) and this solution is passed through a silica column. Elution is carried out with the same mixture of solvents and the eluate is collected in 50 ml fractions. These fractions are examined by thin layer chromatography. Those which contain the desired almost pure ester are combined and the solvent is driven off from them. The residual product is triturated in a mixture of ether and petroleum ether, filtered off and dried. 16.8 g (yield 57%) of 2-(4'-m-trifluoromethylphenyl-piperazino)-ethyl 2-(7'-trifluoromethyl-4'-quinolylamino)-benzoate, melting point 88° to 90°C, are thus isolated.

References

Merck Index 746
DFU 2 (12) 786 (1977)
Kleeman & Engel p. 57
DOT 14 (2) 55 (1978)
I.N. p. 94
Giudicelli, D.P.R.L., Najer, H., Manory, P.M.J. and Dumas, A.P.F.; U.S. Patent 3,935,229; January 27, 1976; assigned to Synthelabo

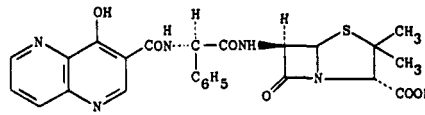
APALCILLIN SODIUM

Therapeutic Function: Antibacterial

Chemical Name: 6-[[[[(4-Hydroxy-1,5-naphthyridin-3-yl)carbonyl] amino] -phenyl acetyl] -amino] -3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] -heptane-2-carboxylic acid

Common Name: D-α-(4-Hydroxy-1,5-naphthyridine-3-carbonamido)benzylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 63469-19-2

Trade Name	Manufacturer	Country	Year Introduced
Lumota	Thomae	W. Germany	1982

Raw Materials

Phenacyl-6-aminopenicillate HCl
D-Phenylglycyl Chloride HCl
4-Hydroxy-1,5-naphthyridine-3-carboxylic acid-N-succinimide ester
Sodium Bicarbonate
Sodium Thiophenoxide
Triethylamine

Manufacturing Process

(a) Preparation of 6-D-α-aminobenzylpenicillin phenacyl ester: To a suspension of phenacyl 6-aminopenicillanate hydrochloride (1.85 g) and D-phenylglycyl chloride hydrochloride (1.29 g) in dichloromethane (20 ml), sodium bicarbonate (1.05 g) was added, and the resultant mixture was stirred while cooling with ice for 6 hours. The reaction mixture was filtered to eliminate the by-produced sodium chloride. The filtrate was admixed with isopropanol and concentrated under reduced pressure by the aid of a rotary evaporator. After the evaporation of dichloromethane, the precipitate was collected by filtration to give the objective compound in the form of the hydrochloride (2.19 g) MP 142° to 148°C (decomposition).

(b) Preparation of D-α-(4-hydroxy-1,5-naphthyridine-3-carbonamido)benzylpenicillin: To a solution of 6-D-α-aminobenzylpenicillin phenacyl ester (hydrochloride) (2.01 g) and triethylamine (0.808 g) in dimethylformamide (20 ml), 4-hydroxy-1,5-naphthyridine-3-carboxylic acid N-succinimide ester [(MP 310° to 311°C (decomposition)] (1.15 g) was added while cooling with ice, and the resultant mixture was stirred for 1 hour. Stirring was further continued at room temperature for 2 hours. After cooling with ice, 1% sodium bicarbonate solution (100 ml) was added thereto. The precipitated crystals were collected by filtration, washed with water and dried over phosphorus pentoxide to give D-(α-4-hydroxy-1,5-naphthyridine-3-carboxamido)benzylpenicillin phenacyl ester (2.17 g).

The above product was dissolved in dimethylformamide (65 ml), sodium thiophenoxide (0.89 g) was added thereto, and the resultant mixture was stirred at room temperature for 1 hour. To the resultant mixture, acetone (650 ml) was added, and the separated crystals were collected by filtration and washed with acetone and ether in order to give the objective compound in the form of the sodium salt (1.3 g).

In the above procedure, the use of 4-hydroxy-1,5-naphthyridine-3-carbonyl chloride in place of 4-hydroxy-1,5-naphthyridine-3-carboxylic acid N-succinimide ester can also afford the same objective compound as above. The use of sodium thio-n-propoxide in place of sodium thiophenoxide can also give the objective compound in the form of the sodium salt.

References

Merck Index 748
DFU 4 (3) 225 (1979)
DOT 19 (2) 110 (1983)
I.N. p. 94
Yamada, H., Tobiki, H., Nakatsuka, I., Tanno, N., Shimago, K. and Nakagome, T.; U.S. Patent 4,005,075; January 25, 1977; assigned to Sumitomo Chemical Co., Ltd.

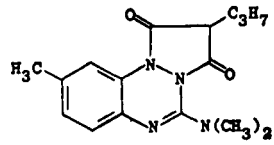
APAZONE

Therapeutic Function: Antiarthritic

Chemical Name: 5-(dimethylamino)-9-methyl-2-propyl-1H-pyrazolo [1,2-a] [1,2,4] benzotriazine-1,3(2H)-dione

Common Name: Azapropazone

Structural Formula:



Chemical Abstracts Registry No.: 113539-59-8

Trade Name	Manufacturer	Country	Year Introduced
Prolixan	Siegfried	W. Germany	1970
Prolixan	Siegfried	Switz.	1970
Cinnamin	Nippon Chemiphar	Japan	1971
Rheumox	Robins	U.K.	1976
Prolixan	Logeais	France	1976
Prolixan	Malesci	Italy	1977
Prolixan	Embil	Turkey	—
Prodisan	Embil	Turkey	—
Prodisan	Roche	—	—
Prolix	Roche	—	—
Prolixano	Leo	—	—
Rheumox	Robins	U.S.	—
Xani	Farmakos	Yugoslavia	—

Raw Materials

3-Dimethylamino-(1,2-Dihydro-1,2,4-benzotriazine)
Diethyl Propyl Malonate
3-Dimethylamino-1,2,4-benzotriazine Oxide
Propyl Malonyl Chloride
Sodium
Hydrogen
Triethylamine

Manufacturing Process

The following describes two alternatives for the synthesis of the closely related butyl analog.

Alternative (a): In a three-neck flask with descending condenser to 3.8 grams of 3-dimethylamino-(1,2-dihydro-1,2,4-benzotriazine) are added 0.52 gram metallic sodium, dissolved in a small volume of absolute alcohol, 4.5 g of diethylbutylmalonate (diethylpropylmalonate for Apazone) and 15 ml of xylene, in a nitrogen atmosphere. The mixture is heated for 2 hours to 70°C, then for 3 hours to 110°-130°C and for one more hour to 150°C, slowly distilling off the alcohol and most of the xylene. To the resulting light brown colored mass are added 200 ml of water. The resulting solution is extracted twice with ether or benzene and afterwards acidified with HCl. Yield 3.6 g of 1,2-butylmalonyl-3-dimethylamino-(1,2-dihydro-1,2,4-benzotriazine). After crystallization from alcohol the melting point is 189°-190°C.

Alternative (b): 3-Dimethylamino-1,2,4-benzotriazine-oxide is shaken in the presence of Raney nickel in 15 volume parts of an alcohol-acetic acid (9:1) mixture in a hydrogen atmosphere. The mixture absorbs 2 mols hydrogen per 1 mol starting material. Hydrogenation can also be effected using a palladium catalyst with a suitable solvent. After reduction it is filtered on a Büchner-funnel through a Hyflow-layer and the solvent is evaporated in vacuo under nitrogen. The residue is dissolved in 20 parts of water-free dioxane and treated at 60°C with the calculated amount of butylmalonyl chloride (propyl malonyl chloride for Apazone) (1 mol/mol) and triethylamine (2 mol/mol). The separated triethylamine hydrochloride is filtered, the dioxane-solution is evaporated under vacuo to dryness, and the residue is dissolved in 7 volume parts of boiling acetic acid. After cooling, the product separates in lightly yellowish crystals. They are dissolved in the calculated amount of 0.25 N NaOH, treated with a small amount of carbon and precipitated with HCl. Melting point of the purified product is 187°C. Yield: approximately 60% of the theoretical amount.

References

Merck Index 750
Kleeman & Engel p. 66
OCDS Vol. 2 p. 475 (1980)
I.N. p. 110
Molnar, I., Wagner-Jauregg, T., Jahn, U. and Mixich, G.; U.S. Patent 3,349,088; October 24, 1967; assigned to Siegfried AG, Switzerland
Molnar, I., Wagner-Jauregg, T., Jahn, U. and Mixich, G.; U.S. Patent 3,482,024; December 2, 1969; assigned to Siegfried AG.

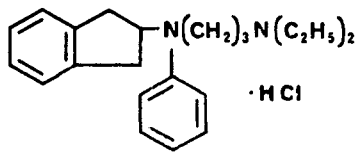
APRINDINE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: N-[3-(Diethylamino)propyl]-N-phenyl-2-indanamine hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 33237-74-0; 37640-71-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Amidonal	Madaus	W. Germany	1976
Fiboran	Sedaph	France	1977
Fibocil	Lilly	U.S.	–
Fiboran	Christiaens	Belgium	–
Ritmusin	Gebro	Austria	–

Raw Materials

N-Phenyl-2-aminoindane
α-Chloropropyl Diethyl Amine
Sodium Hydroxide
Sodium Amide
Hydrogen Chloride

Manufacturing Process

104.6 g (0.5 mol) N-phenyl-2-aminoindane and 2.5 liters benzene are introduced into a reaction vessel of 5 liters, under an atmosphere of nitrogen. 37 g (0.95 mol) sodium amide are added and the mixture is stirred during 3 hours at room temperature.

119.7 g (0.8 mol) of γ-chloropropyl diethylamine are then quickly added. After agitation during 1 hour at room temperature, the reaction mixture is refluxed and stirred under nitrogen during 21 hours. The mixture is then allowed to cool and poured onto ice. The obtained aqueous phase is extracted by means of 500 cm^3 of benzene. The benzene extract is washed two times with 200 cm^3 of water and the benzene is then evaporated.

The residue is treated with 500 cm^3 of hydrochloric acid (2N). The obtained solution is evaporated to dryness and the oily residue is recrystallized from ethanol. 176.9 g (yield 89.4%)

of dihydrochloride of N-phenyl-N-diethylaminopropyl-2-aminoindane are obtained, MP 208° to 210°C.

The dihydrochloride is converted into monohydrochloride by dissolving 26.36 g (0.066 mol) of dihydrochloride into 158 cm^3 of water, adding drop by drop a suitable amount (0.066 mol) of caustic soda (1 N), evaporating the aqueous solution to dryness, drying by means of benzene, filtering the formed sodium chloride (3.8 g) and crystallizing the cooled obtained benzene solution. 22.6 g (95%) of monohydrochloride are obtained, MP 120° to 121°C.

References

Merck Index 776
Kleeman & Engel p. 58
OCDS Vol. 2 p. 208
DOT 10 (4) 120 (1974)
REM p. 860
Vanhoof, P. and Clarebout, P.; British Patent 1,321,424; June 27, 1973; assigned to Manufacture de Produits Pharmaceutiques A. Christiaens, SA

ARGININE GLUTAMATE

Therapeutic Function: Ammonia detoxicant (hepatic failure)

Chemical Name: Glutamic Acid Compound with L-Arginine

Common Name: —

Structural Formula:

$$H_2NC(NH)HN(CH_2)_3CH(NH_2)COOH \cdot HOOC(CH_2)_2(NH_2)COOH$$

Chemical Abstracts Registry No.: 4320-30-3

Trade Name	Manufacturer	Country	Year Introduced
Modamate	Abbott	U.S.	1960
Eucol	Lefranco	France	1970

Raw Materials

L-Arginine
L-Glutamic Acid

Manufacturing Process

This salt may be prepared by mixing L-arginine with L-glutamic acid in water and crystallizing the resulting salt from the water by the addition of a polar water miscible organic solvent to the water. For instance, when 17.2 g of L-arginine and 14.5 g of L-glutamic acid were dissolved in 155 g of water, a clear homogeneous solution resulted which had a pH of 5.3. This solution was filtered and the filtrate was evaporated at 50°C under reduced pressure to a solution having a solids content of about 45%. Absolute methanol (220 g) was added to the concentrated solution of the salt and this mixture cooled to 5°C for one hour. The resulting solid salt was removed from the mixture by filtration and washed with absolute methanol. After being dried preliminarily in the air, the salt was further dried in a vacuum oven at 60°C for 3 hours. The resulting salt, L-arginine-L-glutamate, weighed 30 g (94.6% of the theoretically possible yield based on the amount of L-arginine and L-glutamic acid employed) and melted at 193°–194.5°C with decomposition.

References

Merck Index 798
DFU 3 (1) 10 (1978)
DOT 17 (3) 87 (1981)
I.N. p. 98
Barker, N.G. and Chang, R.W.H., U.S. Patent 2,851,482; September 9, 1958; assigned to General Mills, Inc.

ASPARAGINASE

Therapeutic Function: Antineoplastic (acute leukemia)

Chemical Name: L-Asparagine amidohydrolase

Common Name: Colapase; L-Asnase

Structural Formula:

An enzyme of MW 133,000 ± 5,000 believed to consist of 4 equivalent subunits.

Chemical Abstracts Registry No.: 9015-68-3

Trade Name	Manufacturer	Country	Year Introduced
Crasnitin	Bayer	W. Germany	1969
Crasnitin	Bayer	Italy	1971
Leunase	Kyowa Hakko	Japan	1971
Kidrolase	Specia	France	1971
Crasnitin	Bayer	U.K.	1971
Elspar	Merck Sharp & Dohme	U.S.	1978
Kidrolase	Rhone-Poulenc	Canada	—
Leucogen	Bayer	—	—

Raw Materials

Erwinia bacteria
Nutrient medium

Manufacturing Process

Therapeutically active L-asparaginase is isolated from bacteria from the genus Erwinia, a known genus pathogenic towards plants. L-asparaginase is conveniently isolated from this genus by growing the bacteria upon a suitable nutrient medium until a desired quantity is obtained and then extracting the L-asparaginase either by conventional cell disruption methods, or preferably, by processes more fully described in U.S. Patent 3,660,238.

References

Merck Index 849
Kleeman & Engel p. 62
PDR p. 1176
I.N. p. 102
REM p. 1143
Wade, H.E.; U.S. Patent 3,660,238; May 2, 1972
Herbert, D. and Wade, H.E.; U.S. Patent 3,686,072; August 22, 1972

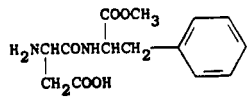
ASPARTAME

Therapeutic Function: Sweetener (dietetic)

Chemical Name: N-L-α-Aspartyl-L-phenylalanine 1-methyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 22839-47-0

Trade Name	Manufacturer	Country	Year Introduced
Canderel	Searle	France	1979
Canderel	Searle	Switz.	1981
Equal	Searle	U.S.	1982
Canderel	Wander	W. Germany	1983
Canderel	Muro	U.S.	–
Nutrasweet	Searle	U.S.	–

Raw Materials

L-Phenylalanine Methyl Ester HCl
N-Benzyloxycarbonyl-L-aspartic acid-α-p-nitrophenyl, β-benzyl Diester
Hydrogen

Manufacturing Process

A solution of 88.5 parts of L-phenylalanine methyl ester hydrochloride in 100 parts of water is neutralized by the addition of dilute aqueous potassium bicarbonate, then is extracted with approximately 900 parts of ethyl acetate. The resulting organic solution is washed with water and dried over anhydrous magnesium sulfate. To that solution is then added 200 parts of N-benzyloxycarbonyl-L-aspartic acid-α-p-nitrophenyl, β-benzyl diester, and that reaction mixture is kept at room temperature for about 24 hours, then at approximately 65°C for about 24 hours. The reaction mixture is cooled to room temperature, diluted with approximately 390 parts of cyclohexane, then cooled to approximately -18°C in order to complete crystallization. The resulting crystalline product is isolated by filtration and dried to afford β-benzyl N-benzyloxycarbonyl-L-aspartyl-L-phenylalanine methyl ester, melting at about 118.5°-119.5°C.

To a solution of 180 parts of β-benzyl N-benzyloxycarbonyl-L-aspartyl-L-phenylalanine methyl ester in 3,000 parts by volume of 75% acetic acid is added 18 parts of palladium black metal catalyst, and the resulting mixture is shaken with hydrogen at atmospheric pressure and room temperature for about 12 hours. The catalyst is removed by filtration, and the solvent is distilled under reduced pressure to afford a solid residue, which is purified by recrystallization from aqueous ethanol to yield L-aspartyl-L-phenylalanine methyl ester. It displays a double melting point at about 190°C and 245°-247°C.

References

Merck Index 852
DOT 16 (2) 65 (1980)
I.N. p. 102
Schlatter, J.M.; U.S. Patent 3,492,131; January 27, 1970; assigned to G.D. Searle & Co.

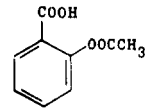
ASPIRIN

Therapeutic Function: Analgesic, antipyretic, antiinflammatory

Chemical Name: 2-(acetyloxy)benzoic acid

Common Name: Acetylsalicylic acid

Structural Formula:



Chemical Abstracts Registry No.: 50-78-2

Trade Name	Manufacturer	Country	Year Introduced
Entab	Mayrand	U.S.	1982
Easprin	WL/PD	U.S.	1982
Ecotrin	Menley James	U.S.	1983
Zorprin	Boots	U.S.	1983
Verin	Verex	U.S.	1983
AAS	Sterwin Espanola	Spain	—
Acesal	Oranienbourg	E. Germany	—
Acetard	Benzon	Denmark	—
Acetisal	Alkaloid	Yugoslavia	—
Acetisal	Farmakos	Yugoslavia	—
Acetisal	Galenika	Yugoslavia	—
Acetical	Rekah	Israel	—
Acetophen	Merck-Frosst	Canada	—
Acetylin	Heyden	W. Germany	—
Acetylo	Chemedica	Switz.	—
Acetylosal	Maria Heil	Austria	—
Acetyl-Sal	Hartz	Canada	—
Acetysal	Jugoremedija	Yugoslavia	—
Acetysal	Krka	Yugoslavia	—
Acetysal	Zdravlje	Yugoslavia	—
Acimetten	Kwieda	Austria	—
Acisal	Pliva	Yugoslavia	—
Adiro	Bayer	—	—
Alaspine	Liba	Turkey	—
Albyl	AFI	Norway	—
Algo	Lokman	Turkey	—
Alka-Seltzer	Miles	Italy	—
Ancasal	Anca	Canada	—
Antidol	Gebro	Austria	—
Apernyl	Bayer	Japan	—
Apyron	Lingner & Fischer	W. Germany	—
Asart	SK&F	U.S.	—
Asatard	De Angeli	Italy	—
Asdol	Srbolek	Yugoslavia	—
Aspalgin	Krka	Yugoslavia	—
Aspec	Kempthorne Prosser	New Zealand	—
Aspegic	Egic	France	—
Aspercin	Otis Clapp	U.S.	—
Aspermin	Buffington	U.S.	—
Aspirin	Bayer	W. Germany	—

Trade Name	Manufacturer	Country	Year Introduced
Aspirtab	Dover	U.S.	–
Aspirvess	Miles	U.S.	–
Aspisol	Bayer	W. Germany	–
Aspro	Nicholas	Italy	–
Aspro	Pan Quimica	Spain	–
Asrivo	Rivopharm	Switz.	–
Astrin	Medic	Canada	–
Ataspin	Atabay	Turkey	–
Babypyrin	Pfizer	U.S.	–
Bebaspin	Deva	Turkey	–
Bi-Prin	Boots	U.K.	–
Breoprin	Izal	U.K.	–
Bufacyl	Teva	Israel	–
Buffaprin	Buffington	U.S.	–
Buffasal	Dover	U.S.	–
Calmo Yer	Yer	Spain	–
Caprin	Sinclair	U.K.	–
Casprium	Liade	Spain	–
Catalgine	Theraplix	France	–
Cedrox	Cederroths	Sweden	–
Cemerit	Bayer	Italy	–
Claradin	Nicholas	U.K.	–
Claragine	Nicholas	France	–
Clariprin	Nicholas	–	–
Codalgina	Fass	Spain	–
Colfarit	Bayer	W. Germany	–
Contrheuma-Retard	Spitzner	W. Germany	–
Coryphen	Rougier	Canada	–
Diaforil	Maggioni	Italy	–
Domupirina	Medici Domus	Italy	–
Ecasil	Andromacco	Argentina	–
Ecoprin	Sam-On	Israel	–
Ecotrin	SK&F	U.S.	–
Empirin	Burroughs-Wellcome	U.S.	–
Endospirin	Enila-Lotecia	Brazil	–
Endyol	Guidotti	Italy	–
Entericin	Bristol-Myers	U.S.	–
Enterosarine	Sarein	France	–
Entrophen	Merck-Frosst	Canada	–
Eskotrin	SK&F	U.S.	–
Extren	Vicks	U.S.	–
Flectadol	Maggioni	Italy	–
Genasprin	Fisons	U.K.	–
Godamed	Pfleger	W. Germany	–
Globentyl	Nyegaard	Norway	–
Globoid	Nyegaard	Norway	–
Glucetyl	Technicopharm	Switz.	–
Hagedabletten	Hageda	W. Germany	–
Halgon	Togal	W. Germany	–
Idotyl	Ferrosan	Denmark	–
Juveprine	Sarget	France	–
Kilios	Farmitalia Carlo Erba	Italy	–
Levius	Pharmitalia	U.K.	–
Levius	Montedison	W. Germany	–
Licyl	A.L.	Norway	–
Longasa	Squibb	U.S.	–
Magnecyl	ACO	Sweden	–

Trade Name	Manufacturer	Country	Year Introduced
Magnyl	DAK	Denmark	–
Measurin	Breon	U.S.	–
Medisyl	Medica	Finland	–
Mejoral Infantil	Sterwin Espanola	Spain	–
Micristin	Gyogyert	Hungary	–
Neopirine	Casgrain & Charbonneau	Canada	–
Neutracetyl	Promedica	France	–
Nibol	Bosnalijek	Yugoslavia	–
Nova-Phase	Nova	Canada	–
Novasen	Novopharm	Canada	–
Pharmacin	Optrex	U.K.	–
Premaspin	Laake	Finland	–
Pyronoval	Hoechst	W. Germany	–
Rectosalyl	Bouty	Italy	–
Reunyl	Hassle	Sweden	–
Rhodine	Specia	France	–
Rhonal	Specia	France	–
Rhonal	Rhodia Iberica	Spain	–
Rhusal	G.P.	Australia	–
Riphen	Riva	Canada	–
Rodina	Farmitalia Carlo Erba	Italy	–
Sal Adult	Beecham	U.K.	–
Sal Infant	Beecham	U.K.	–
Sargepirine	Sarget	France	–
Saspryl	Teva	Israel	–
Seclopyrine	Seclo	France	–
Servisprin	Servipharm	Switz.	–
Solprin	Reckitt	U.K.	–
Solpyron	Beecham	U.K.	–
Solucetyl	Sarback	France	–
Solusal	Hamilton	Australia	–
St. Joseph	Plough	U.S.	–
Supasa	Nordic	Canada	–
Tasprin	Ticen	U.K.	–
Temagin	Beiersdorf	W. Germany	–
Triaphen	Trianon	Canada	–
Trineral	Beiersdorf	W. Germany	–
Winsprin	Winthrop	U.S.	–

Raw Materials

Salicylic Acid
Acetic Anhydride
Ketene

Manufacturing Process

As described in U.S. Patent 2,731,492, a glass-lined reactor of 1,500 gallons capacity, fitted with a water-cooled reflux condenser, thermometers with automatic temperature registers and an efficient agitator, is employed.

To start the process, a mother liquor is made by dissolving 1,532 kg of acetic anhydride (15 mols) in 1,200 kg of toluene. To this mother liquor, add 1,382 kg of salicylic acid (10 mols), heat the reaction mixture under an efficient reflux condenser, to 88°-92°C and maintain within this temperature range for 20 hours.

The reaction mixture is now transferred to aluminum cooling tanks, and is allowed to cool slowly, over a period of 3 to 4 days, to a terminal temperature of 15°-25°C (room tempera-

ture). The acetylsalicylic acid precipitates as large, regular crystals. The mother liquor is now filtered or centrifuged from the precipitated acetylsalicylic acid and the filter cake is pressed or centrifuged as free of mother liquor as possible. The crystals are washed with distilled water until completely free of acetic acid, pressed or centrifuged as dry as possible and the filter cake is then dried in a current of warm air at a temperature of 60°-70°C.

The filtrate from this first batch will comprise a solution of 180 to 270 kg of unprecipitated acetylsalicylic acid (1.0 to 1.5 mols), 510 kg of acetic anhydrice (5.0 mols), 600 kg of acetic acid (10.0 mols) (obtained as a by-product in the acetylation step) and 1,200 kg of the diluent toluene. Into this filtrate, at a temperature of 15° to 25°C, ketene gas is now passed through a sparger tube or diffuser plate, with good agitation, until a weight increase of 420.5 kg of ketene (10 mols) occurs. The reaction mixture will now contain 180-270 kg of unprecipitated acetylsalicylic acid (1.0-1.5 mols) and 1,532 kg of acetic anhydride (15 mols) in 1,200 kg of toluene. This mother liquor is recycled to the first step of the process for reaction with another batch of 1,382 kg of salicylic acid. On recirculating the mother liquor, the yield of pure acetylsalicylic acid is 1,780 to 1,795 kg per batch.

References

Merck Index 863
Kleeman & Engel p. 12
PDR (Many References)
DOT 16 (10) 359 (1980)
REM p. 1112
Kamlet, J.; U.S. Patent 2,731,492; January 17, 1956
Hamer, W.E. and Phillips, G.V.; U.S. Patent 2,890,240; June 9, 1959; assigned to Monsantc Chemicals, Limited, England
Edmunds, R.T.; U.S. Patent 3,235,583; February 15, 1966; assigned to The Norwich Pharmacal Company

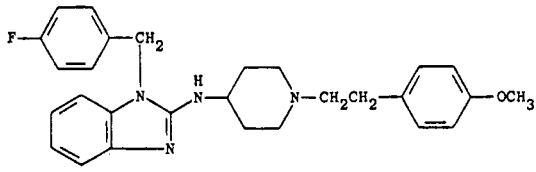
ASTEMIZOLE

Therapeutic Function: Antiallergic; antihistaminic

Chemical Name: 1-[(4-Fluorophenyl)methyl]-N-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Hismanal	Janssen	U.K.	1983

Raw Materials

2-(4-Methoxyphenyl)ethyl Methane Sulfonate

1-[(4-Fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine Dihydrobromide
Sodium Carbonate

Manufacturing Process

A mixture of 2.3 parts of 2-(4-methoxyphenyl)ethyl methanesulfonate, 4.9 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 3.2 parts of sodium carbonate, 0.1 part of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70°C. The reaction mixture is poured onto water. The product is extracted with methylbenzene. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2'-oxybispropane, yielding 2.2 parts (48%) of 1-(4-fluorophenylmethyl)-N-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine; MP 149.1°C.

References

Merck Index A-1
DFU 7 (1) 10 (1982)
OCDS Vol. 3 p. 177
DOT 19 (7) 412 (1983)
I.N. p. 102
Janssens, F., Stokbroekx, R., Torremans, J. and Luyckx, M; U.S. Patent 4,219,559; August 26, 1980; assigned to Janssen Pharmaceutica N.V.

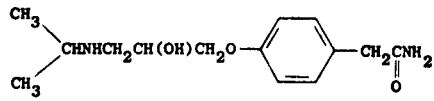
ATENOLOL

Therapeutic Function: β-Adrenergic blocking drug

Chemical Name: 4-[2-hydroxy-3-[(1-methylethyl)amino] propoxy] benzeneacetamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 29122-68-7

Trade Name	Manufacturer	Country	Year Introduced
Tenormin	Stuart	U.K.	1976
Tenormin	I.C.I.	W. Germany	1976
Tenormin	I.C.I.	Switz.	1978
Tenormin	I.C.I.	Italy	1979
Tenormin	I.C.I.	France	1979
Tenormin	Stuart	U.S.	1981
Atenol	C.T.	Italy	—
Blokium	Prodes	Spain	—
Ibinolo	I.B.I.	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
Myocord	Szabo-Kessler	Argentina	–
Normiten	Abic	Israel	–
Seles Beta	Farmitalia Carlo Erba	Italy	–
Tenoretic	Stuart	U.S.	–
Vericordin	Lazar	Argentina	–

Raw Materials

p-Hydroxyphenylacetamide
Epichlorohydrin
Isopropylamine

Manufacturing Process

1 gram of 1-p-carbamoylmethylphenoxy-2,3-epoxypropane and 10 ml of isopropylamine in 25 ml of methanol is heated in a sealed tube at 110°C for 12 hours. The mixture is evaporated to dryness and the residue is partitioned between 50 ml of chloroform and 50 ml of aqueous 2N-hydrochloric acid. The aqueous acidic layer is separated, made alkaline with sodium carbonate and extracted twice with 50 ml of chloroform each time. The combined extracts are dried and evaporated to dryness and the residue is crystallized from ethyl acetate. There is thus obtained 1-p-carbamoylmethylphenoxy-3-isopropylamino-2-propanol, MP 146°–148°C.

The 1-p-carbamoylmethylphenoxy-2,3-epoxypropane used as starting material may be obtained as follows: a mixture of 3.2 grams of p-hydroxyphenylacetamide, 25 ml of epichlorohydrin and 6 drops of piperidine is heated at 95°–100°C for 6 hours. The mixture is cooled and filtered and the solid product is crystallized from methanol. There is thus obtained 1-p-carbamoylmethylphenoxy-2,3-epoxypropane, MP 158°–160°C.

References

Merck Index 868
DFU 1 (1) 7 (1976)
Kleeman & Engel p. 62
PDR pp. 1786, 1788
OCDS Vol. 2 p. 109 (1980)
DOT 13 (2) 49 (1977) & 16 (1) 30 (1980)
I.N. p. 103
REM p. 904
Barrett, A.M., Carter, J., Hull, R., Le Count, D.J. and Squire, C.J.; U.S. Patent 3,663,607; May 16, 1972; assigned to Imperial Chemical Industries Limited, England
Barrett, A.M., Carter, J., Hull, R., Le Count, D.J. and Squire, C.J.; U.S. Patent 3,836,671; September 17, 1974; assigned to Imperial Chemical Industries Limited, England

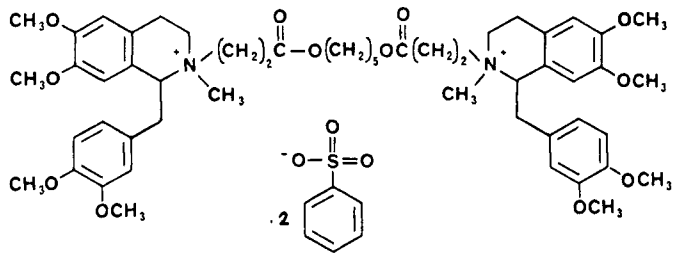
ATRACURIUM BESYLATE

Therapeutic Functon: *Neuromuscular blocker*

Chemical Name: N,N'-4,10-dioxa-3,11-dioxotridecylene-1,13-bis-tetrahydropapaverine dibenzenesulfonate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 64228-81-5

Trade Name	Manufacturer	Country	Year Introduced
Tracrium	Burroughs Wellcome	U.S.	1983
Tracrium	Burroughs Wellcome	U.K.	1983
Tracrium	Burroughs Wellcome	Switz.	1983

Raw Materials

Acryloyl Chloride
Pentane-1,5-diol
Tetrahydropapaverine
Methyl Benzene Sulfonate

Manufacturing Process

Acryloyl chloride (0.2 mol) in dry benzene (60 ml) was added over 0.5 hour with mechanical stirring to pentane-1,5-diol (0.1 mol), triethylamine (0.2 mol) and pyrogallol (0.1 g) in dry benzene (100 ml). Further dry benzene (ca 100 ml) was added followed by triethylamine (10 ml), and the mixture stirred at 50°C for 0.5 hour. The triethylamine hydrochloride was filtered off and the solvent removed in vacuo to leave a yellow oil which was distilled in the presence of a trace of p-methoxyphenol, excluding light, to give 1,5-pentamethylene diacrylate (12.9 g; 61%; BP 90° to 95°C/0.01 mm Hg).

A solution of tetrahydropapaverine (4.43 g) and 1,5-pentamethylene diacrylate (1.30 g) in dry benzene (15 ml) was stirred under reflux for 48 hours excluding light. The solvent was removed in vacuo and the residual pale red oil dissolved in chloroform (10 ml). Addition of ether (ca 400 ml), followed by saturated ethereal oxalic acid solution (ca 500 ml) gave a flocculent white precipitate, which was filtered off, washed with ether and dried. Crystallization (twice) from ethanol gave N,N'-4,10-dioxa-3,11-dioxotridecylene-1,13-bis-tetrahydropapaverine dioxalate as a white powder (3.5 g; 51%; MP 117° to 121°C).

The free base, N,N'-4,10-dioxa-3,11-dioxotridecylene-1,13-bis-tetrahydropapaverine, was obtained by basifying an aqueous solution of the dioxalate with sodium bicarbonate solution, followed by extraction with toluene and evaporation of the solvent, to give a colorless viscous oil.

Scrupulously dried base (0.5 g) in spectroscopically pure acetonitrile (8 ml) was treated with methyl benzene sulfonate at room temperature for 22 hours. The filtered reaction mixture was added dropwise to mechanically stirred, filtered, dry ether (ca 450 ml). The flocculent white precipitate was filtered off, washed with dry ether, and dried in vacuo over P_2O_5 at 50°C to yield the product, an off-white powder melting at 85° to 90°C.

References

Merck Index A-2
DFU 5 (11) 541 (1980)
PDR p. 766

DOT 19 (2) 111 (1983)
I.N. p. 104
REM p. 925
Stenlake, J.B., Waigh, R.D., Dewar, G.H., Urwin, J. and Dhar, N.C.; U.S. Patent 4,179,507 December 18, 1979; assigned to Burroughs Wellcome Company

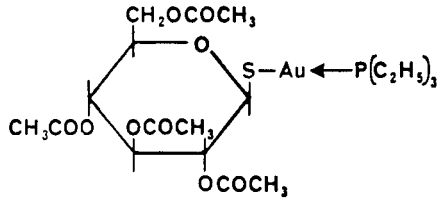
AURANOFIN

Therapeutic Function: Antiarthritic

Chemical Name: S-Triethylphosphinegold 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 34031-32-8

Trade Name	Manufacturer	Country	Year Introduced
Ridaura	SK&F	W. Germany	1982
Ridaura	SK&F	Switz.	1983

Raw Materials

Thiodiglycol
Triethylphosphine
S-(2,3,4,6-Tetra-O-acetylglucopyranosyl)thiopseudourea Hydrobromide
Gold Acid Chloride Trihydrate
Potassium Carbonate

Manufacturing Process

(A) Triethylphosphinegold chloride: A solution of 10.0 g (0.08 mol) of thiodiglycol in 25 ml of ethanol is mixed with a solution of 15.76 g (0.04 mol) of gold acid chloride trihydrate in 75 ml of distilled water. When the bright orange-yellow solution is almost colorless, it is cooled to -5°C and an equally cold solution of 5.0 g (0.0425 mol) of triethylphosphine in 25 ml of ethanol is added dropwise to the stirred solution. After the addition is complete, the cooled mixture is stirred for ½ hour. Solid that separates is removed and the filtrate is concentrated to about 30 ml to yield a second crop. The combined solid is washed with aqueous-ethanol (2:1) and recrystallized from ethanol by adding water to the cloud point. The product is obtained as white needles, MP 85° to 86°C.

(B) Auranofin: A cold solution of 1.66 g (0.012 mol) of potassium carbonate in 20 ml of distilled water is added to a solution of 5.3 g (0.011 mol) of S-(2,3,4,6-tetra-O-acetylglucopyranosyl)-thiopseudourea hydrobromide [*Methods in Carbohydrate Chemistry,* vol 2, page 435 (1963)] in 30 ml of water at -10°C. A cold solution of 3.86 g (0.011 mol) of triethylphosphinegold chloride in 30 ml of ethanol containing a few drops of methylene chloride is added to the above mixture before hydrolysis of the thiouronium salt is complete. After the addition is complete, the mixture is stirred in the cold for ½ hour. The solid that separates

is removed, washed first with aqueous ethanol then water and dried in vacuo. There is obtained colorless crystals, MP 110° to 111°C, of S-triethylphosphinegold 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside.

References

Merck Index 882
DFU 1 (10) 451 (1976)
PDR p. 1721
DOT 18 (9) 463 (1982)
I.N. p. 106
REM p. 1122
McGusty, E.R. and Sutton, B.M.; U.S. Patent 3,708,579; January 2, 1973; assigned to Smith Kline and French Laboratories
Nemeth, P.E. and Sutton, B.M.; U.S. Patent 3,635,945; January 18, 1972; assigned to Smith Kline and French Laboratories

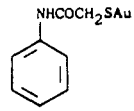
AUROTHIOGLYCANIDE

Therapeutic Function: Antiarthritic

Chemical Name: [[(Phenylcarbamoyl)methyl] thio] gold

Chemical Name: Aurothioglycollic acid anilide

Structural Formula:



Chemical Abstracts Registry No.: 16925-51-2

Trade Name	Manufacturer	Country	Year Introduced
Lauron	Endo	U.S.	1945

Raw Materials

Potassium Bromoaurate
Sulfur Dioxide
Thioglycolic Acid Anilide

Manufacturing Process

The product is made preferably by reacting thioglycolic-acid-anilide with an aurous bromide (AuBr).

Prior art methods for making the starting material, $HSCH_2CONHC_6H_5$ are disclosed in an article by Beckurts et al. in *Journ. Praktische Chemie* (2) 66 p. 174, and in the literature referred to in the mentioned article.

Ten grams of the potassium salt of bromoauric acid ($KBrA_4$) are dissolved in 100 cc of 96% ethyl alcohol. This salt is also designated as potassium auribromide. Sulfur dioxide (SO_2) is then led through this solution, through a fine capillary tube, for several minutes. This reaction produces aurous bromide (AuBr). The solution of the aurous bromide is then allowed to

stand for 2 to 3 hours until it is colorless. A precipitate of KBr is thus formed. This precipitate is separated from the solution of the aurous bromide which is added to a solution of three grams of the thioglycolic-acidanilide in 50 cc of ethyl alcohol. This is done at about 20°C. Then 300 cc of water are added to this mixture, at 20°C. The water is then removed by decantation or any suitable method, and the mixture is repeatedly thus treated with water, in order to remove all impurities which can thus be removed. The product is then centrifuged twice with 96% ethyl alcohol. It is then centrifuged three times with 100% or absolute ethyl alcohol, and then centrifuged three times with water-free ligroin (petroleum ether), i.e., the 40°-60°C fraction which is distilled from petroleum. After each centrifuging, the product is separated from the liquid which has been used during the centrifuging.

The product is then dried in a high vacuum with the use of phosphorus pentoxide (P_2O_5).

References

Merck Index 889
I.N. p. 106
Lewenstein, M.J.; U.S. Patent 2,451,841; October 19, 1948

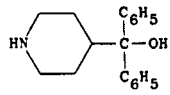
AZACYCLONOL

Therapeutic Function: Tranquilizer

Chemical Name: α,α-Diphenyl-4-piperidinemethanol

Common Name: Gamma-pipradol

Structural Formula:



Chemical Abstracts Registry No.: 115-46-8; 1798-50-1 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Frenquel	Merrell	U.S.	1955
Frenoton	Draco	Sweden	—
Frenquel	Inibsa	Spain	—
Frenquel	Merrell-Toraude	France	—
Frenquel	Shionogi	Japan	—

Raw Materials

α-(4-Pyridyl)-benzhydrol
Hydrogen

Manufacturing Process

A mixture of 26 g (0.1 mol) of α-(4-pyridyl)-benzhydrol, 1.5 g of platinum oxide, and 250 ml of glacial acetic acid is shaken at 50°-60°C under hydrogen at a pressure of 40-50 lb/in^2. The hydrogenation is complete in 2 to 3 hours. The solution is filtered and the filtrate evaporated under reduced pressure. The residue is dissolved in a mixture of equal parts of methanol and butanone and 0.1 mol of concentrated hydrochloric acid is added. The mixture is cooled and filtered to give about 30 g of α-(4-piperidyl)-benzhydrol hydrochloride, MP 283°-285°C, as a white, crystalline substance.

The free base is readily obtained from the hydrochloride salt by treatment with ammonia and when so obtained has a melting point of 160°-161°C.

References

Merck Index 898
Kleeman & Engel p. 65
OCDS Vol. 1 p. 47
I.N. p. 109
Schumann, E.L., Van Campen, M.G., Jr. and Pogge, R.C.; U.S. Patent 2,804,422; August 27, 1957; assigned to The Wm. S. Merrell Co.

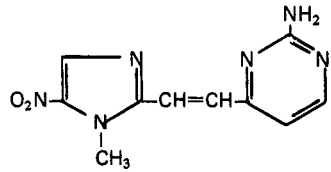
AZANIDAZOLE

Therapeutic Function: Antiprotozoal, antibacterial

Chemical Name: 2-Amino-4-[2-(1-methyl-5-nitroimidazol-2-yl)vinyl] pyrimidine

Common Name: Nitromidine

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Triclose	Ist. Chemioter.	Italy	1977
Triclose	I.C.I.	Italy	–

Raw Materials

2-Amino-4-methylpyrimidine
2-Formyl-1-methyl-5-nitroimidazole
Sulfuric Acid

Manufacturing Process

Into a mixture of 1.6 g of 2-amino-4-methylpyrimidine with 10 ml of glacial acetic acid is slowly added 2.13 g of concentrated sulfuric acid. A mixture of 2.4 g of 2-formyl-1-methyl-5-nitroimidazole in 20 ml of glacial acetic acid is slowly added to the mixture of the pyrimidine under stirring. The reaction mixture is maintained at a temperature of about 55°C for 4 hours. The resultant mixture is then diluted with 200 ml of distilled water and neutralized with a saturated aqueous solution of sodium bicarbonate. A brownish-yellow precipitate (MP 232° to 235°C) is formed and recovered. The product is analyzed by infrared spectroscopy and is found to conform to 2-amino-4-[2-(1-methyl-5-nitro-2-imidazolyl)vinyl] pyrimidine.

References

Merck Index 902
DOT 14 (6) 234 (1978)

I.N. p. 109
Garzia, A.; U.S. Patent 3,882,105; May 6, 1975; assigned to Istituto Chemioterapico Italiano SpA
Garzia, A.; U.S. Patent 3,969,520; July 13, 1976; assigned to Istituto Chemioterapico Italiano SpA

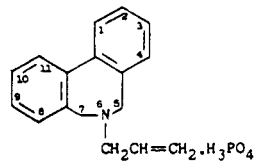
AZAPETINE PHOSPHATE

Therapeutic Function: Antiadrenergic

Chemical Name: 6,7-Dihydro-6-(2-propenyl)-5H-dibenz[c,e]-azepine phosphate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 130-83-6; 146-36-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ilidar	Roche	U.S.	1954
Ilidar	Roche	W. Germany	–

Raw Materials

Diphenic Acid
Ammonia
Lithium Aluminum Hydride
Acetic Anhydride
Allyl Bromide
Phosphoric Acid

Manufacturing Process

29 grams of diphenic acid were stirred in 900 cc of acetic anhydride at 120°C for one hour. The cooled mixture was filtered and washed with acetic acid to give diphenic anhydride, colorless crystals, MP about 222°-226°C.

24.11 grams of diphenic anhydride were mixed with 50 cc of concentrated ammonia. The mixture warmed up and cooling was applied, after which the mixture was stirred until a clear solution formed and for 1½ hours afterward. The mixture was acidified and allowed to stand overnight. Water was added, initiating precipitation. The mixture was chilled and filtered to yield diphenamic acid, a colorless solid, MP about 191°-193°C.

23.5 grams of diphenamic acid were heated at 200°C in an oil bath, first for about 20 hours at atmospheric pressure and then for about 10 hours at about 20 mm.

Melting points were taken at intervals in order to gain an idea of the extent of reaction. The final residue was boiled with alcohol but since the solid exhibited insufficient solubility in the hot solvent, the mixture was filtered. The residue consisted of tan crystals, MP about 220°-221°C, and the filtrate on cooling gave an additional crop of tan crystals, MP about 219°-221°C. The two materials were identical and consisted of diphenimide.

5.58 g of diphenimide were placed in a Soxhlet thimble and extracted for about 3 days with a boiling mixture of 9.0 g of lithium aluminum hydride in 600 cc of sodium-dried ether. Excess lithium aluminum hydride was then decomposed cautiously with water and the mixture was filtered through a filter aid by suction. The filtrate consisted of two layers. The ether layer was separated and dried with anhydrous potassium carbonate and acidified with alcoholic hydrochloric acid to give 6,7-dihydro-5H-dibenz[c,e] azephine hydrochloride, MP about 287°-289°C.

One gram of 6,7-dihydro-5H-dibenz[c,e] azepine hydrochloride was dissolved in water, made alkaline with concentrated ammonia, and the resultant base extracted twice with benzene. The benzene layers were combined, dried with anhydrous potassium carbonate, and mixed with 0.261 g of allyl bromide at 25°-30°C. The reaction solution became turbid within a few minutes and showed a considerable crystalline deposit after standing 3½ days. The mixture was warmed 1¾ hours on the steam bath in a loosely-stoppered flask, then cooled and filtered. The filtrate was washed twice with water and the benzene layer evaporated at diminished pressure. The liquid residue was dissolved in alcohol, shaken with charcoal and filtered. Addition to the filtrate of 0.3 gram of 85% phosphoric acid in alcohol gave a clear solution which, when seeded and rubbed, yielded 6-allyl-6,7-dihydro-5H-dibenz[c,e] azepine phosphate, MP about 211°-215°C with decomposition.

References

Merck Index 904
Kleeman & Engel p. 65
I.N. p. 109
Schmidt, R.A. and Wenner, W.; U.S. Patent 2,693,465; November 2, 1954; assigned to Hoffmann-La Roche, Inc.

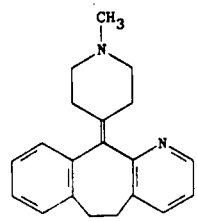
AZATADINE MALEATE

Therapeutic Function: Antihistaminic

Chemical Name: 6,11-Dihydro-11-(1-methyl-4-piperidinylidene)-5H-benzo[5,6] cyclohepta-[1,2-b] pyridine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 3978-86-7

Trade Name	Manufacturer	Country	Year Introduced
Idulian	Unilabo	France	1968
Optimine	Schering	U.S.	1977
Optimine	Warrick	U.K.	1978
Optimine	Warrick	Italy	1983

Trade Name	Manufacturer	Country	Year Introduced
Optimine	Byk Essex	W. Germany	1983
Trinalin	Schering	U.S.	—
Verben	Schering	—	—
Zadine	Schering	—	—

Raw Materials

N-Methyl-4-chloropiperidine
Polyphosphoric Acid
4-Aza-10,11-dihydro-5-H-dibenzo-[a,d]-cycloheptene-5 one
Ethyl Bromide
Magnesium
Maleic Acid

Manufacturing Process

Preparation of 4-aza-5-(N-methyl-4-piperidyl)-10,11-dihydro-5H-dibenzo[a,d] cycloheptene-5-ol: Add 17.4 g of N-methyl-4-chloropiperidine to a stirred mixture containing 3.2 g of magnesium, 20 ml of anhydrous tetrahydrofuran, 1 ml of ethyl bromide and a crystal of iodine. Reflux for two hours, cool to 30°–35°C and add a solution of 13 g of 4-aza-10,11-dihydro-5H-dibenzo[a,d] cycloheptene-5-one in 25 ml of tetrahydrofuran. Stir for five hours, remove the solvent by distillation in vacuo and add 250 ml of ether. Add 100 ml of 10% ammonium chloride solution and extract the mixture with chloroform. Concentrate the chloroform solution to a residue and recrystallize from isopropyl ether obtaining 20 g of the carbinol, MP 173°–174°C.

Preparation of 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d] cycloheptene: Heat 5.4 g of the carbinol and 270 g of polyphosphoric acid for 12 hours at 140°–170°C. Pour into ice water and make alkaline with sodium hydroxide. Extract with ether. Dry ether solution and concentrate to a residue. Crystallize from isopropyl ether, MP 124°–126°C.

Preparation of 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d] cycloheptene dimaleate: To a solution containing 4.3 g of 4-aza-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d] cycloheptene in 55 ml of ethyl acetate, add a solution of 3.45 g of maleic acid dissolved in ethyl acetate. Filter the resulting precipitate and recrystallize the desired product from an ethyl acetate-methanol mixture to yield 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d] cycloheptene dimaleate, MP 152°–154°C.

References

Merck Index 906
PDR pp. 1643, 1657
OCDS Vol. 2 p. 424
DOT 5 (2) 47 (1969)
I.N. p. 110
REM p. 1131
Villani, F.J.; U.S. Patents 3,326,924; January 20, 1967; 3,357,986; December 12, 1967; and 3,419,565; December 31, 1968; all assigned to Schering Corp.

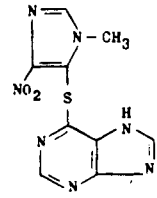
AZATHIOPRINE

Therapeutic Function: Immunosuppressive

Chemical Name: 6-[(1-methyl-4-nitroimidazol-5-yl)thio] purine

Common Name: Azothioprine

Structural Formula:



Chemical Abstracts Registry No.: 446-86-6

Trade Name	Manufacturer	Country	Year Introduced
Imuran	Wellcome	U.K.	1964
Imurel	Wellcome	France	1967
Imurek	Wellcome	W. Germany	1967
Imuran	Wellcome	U.S.	1968
Imuran	Wellcome	Italy	1968
Imuran	Tanabe	Japan	1969
Azamun	Medica	Finland	—
Azanin	Tanabe	Japan	—
Azapress	Lennon	South Africa	—

Raw Materials

N,N'-Dimethyloxaldiamide
Phosphorus Pentachloride
Nitric Acid
6-Mercaptopurine

Manufacturing Process

N,N'-dimethyloxaldiamide is reacted with PCl_5 to give 4-chloro-1-methyl imidazole. This is nitrated with HNO_3 to give 5-nitro-1-methyl-4-chloroimidazole. Then, a mixture of 4.6 grams of anhydrous 6-mercaptopurine, 5 grams of 1-methyl-4-chloro-5-nitroimidazole and 2.5 grams of anhydrous sodium acetate in 100 ml of dry dimethyl sulfoxide was heated at 100°C for 7 hours.

After standing overnight at room temperature, the mixture was poured into 200 ml of cold water and the yellow precipitate of 6-(1'-methyl-4'-nitro-5'-imidazolyl)mercaptopurine (7.0 grams) collected. After recrystallization from 50 % aqueous acetone, the product melted at 243°-244°, dec., and had an UV spectrum with λ maximum = 280 mμ at pH 1 and λ max. = 285 mμ at pH 11.

References

Merck Index 907
Kleeman & Engel p. 67
PDR p. 744
OCDS Vol. 2 p. 464
DOT 16 (10) 360 (1980)
I.N. p. 110
REM p. 1143
Hitchings, G.H. and Elion, G.B.; U.S. Patent 3,056,785; October 2, 1962; assigned to Burroughs Wellcome & Co.

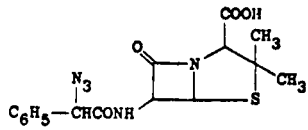
AZIDOCILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-(D-2-azido-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0] heptane-2-carboxylic acid

Common Name: α-Azidobenzylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 17243-38-8

Trade Name	Manufacturer	Country	Year Introduced
Nalpen	Beecham	W. Germany	1972
Longatren	Bayer	Italy	1981
Longatren	Bayer	Japan	–
Astracilina	Astra	Sweden	–
Finacillin	Sedequil	Portugal	–
Syncillin	Tropon	W. Germany	–

Raw Materials

α-Azidophenylacetic Acid
Ethyl Chloroformate
6-Aminopenicillanic Acid
Triethylamine
Thionyl Chloride

Manufacturing Process

Example 1: α-Azidobenzylpenicillin via the Mixed Anhydride — A solution of α-azidophenylacetic acid (8.9 grams, 0.05 mol) of triethylamine (5.1 grams, 0.05 mol) in 50 ml of dry dimethylformamide was stirred and chilled below -5°C. At this temperature ethyl chloroformate (4.7 ml) was added in portions so that the temperature was never above -5°C. After the mixture had been stirred for 20 minutes, dry acetone (100 ml), chilled to -5°C, was added in one portion, immediately followed by an ice-cold solution of 6-aminopenicillanic acid (10.8 grams, 0.05 mol) and triethylamine (5.1 grams, 0.05 mol) in 100 ml of water, and the stirring was continued for 1½ hours at 0°C.

The pH of the mixture was adjusted to 7.5 by adding a saturated sodium bicarbonate solution. After being washed twice with diethyl ether, the reaction solution was acidified to pH 2 with dilute hydrochloric acid and extracted with ether. The ether solution containing the free penicillin was washed twice with water and then extracted with 50 ml of N potassium bicarbonate solution. After freeze drying of the obtained neutral solution, the potassium salt of α-azidobenzylpenicillin was obtained as a slightly colored powder (11.2 grams, 54% yield) with a purity of 55% as determined by the hydroxylamine method (the potassium salt of penicillin G being used as a standard).

The infrared spectrum of this substance showed the presence of an azido group and a β-lactam system. The substance inhibited the growth of *Staph. aureus* Oxford at a concentration of 0.25 mcg/ml.

Example 2: α-Azidobenzylpenicillin via the Acid Chloride — 6-aminopenicillanic acid (18.5 grams, 0.085 mol) and sodium bicarbonate (21 grams, 0.025 mol) were dissolved in 200 ml of water and 100 ml of acetone. To this solution, chilled in ice, was added α-azidophenylacetyl chloride (16.6 grams, 0.085 mol), diluted with 10 ml of dry acetone. The temperature is held at 0° to 5°C and the reaction mixture was stirred for 2½ hours.

The resulting solution was treated as described in Example 1 to give the potassium salt of

α-azidobenzylpenicillin as a white powder (29.4 grams, 84% yield) with a purity of 83% as determined by the hydroxylamine method (the potassium salt of penicillin G being used as a standard).

The product showed the same properties as the product obtained in Example 1; it inhibits the growth of *Staph. aureus* Oxford at a concentration of 0.13 mcg/ml.

The α-azidophenylacetyl chloride was prepared by treating α-azidophenylacetic acid with thionylchloride in portions at room temperature and then heating the solution under reflux for one hour. The α-azidophenylacetyl chloride distils at 115°C under a pressure of 10 mm Hg.

References

Merck Index 913
Kleeman & Engel p. 68
DOT 7 (5) 186 (1971 & 8 (7) 248 (1972)
I.N.p. 111
Sjoberg, B.O.H. and Ekstrom, B.A.; U.S. Patent 3,293,242; December 20, 1966; assigned to Beecham Group Limited, England

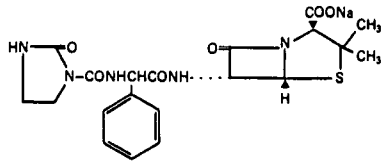
AZLOCILLIN

Therapeutic Function: Antibacterial

Chemical Name: D-α-(imidazolidin-2-on-1-yl-carbonylamino)benzylpenicillin, sodium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 37091-66-0; 37091-65-9 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Securopen	Bayer	W. Germany	1977
Securopen	Bayer	Switz.	1980
Securopen	Bayer	U.K.	1980
Azlin	Miles	U.S.	1982
Securopen	Bayer	France	1983

Raw Materials

D(–)-α-[(Imidazolidin-2-on-1-yl)carbonylamino]phenyl Acetic Acid
6-Aminopenicillanic Acid

Manufacturing Process

3.8 parts by weight of D(–)-α-[(imidazolidin-2-on-1-yl)carbonylamino]phenyl-acetic acid were dissolved in 65 parts by volume of dichloromethane. 2.7 parts by weight of 1-methyl-2-chloro-

Δ1-pyrrolinium chloride were added, and after cooling to -10°C 2.0 parts by volume of triethylamine were added gradually. This reaction mixture was then stirred for one hour at -5°C (mixture A). 4.0 parts by weight of 6-aminopenicillanic acid in 80 parts by volume of dichloromethane were treated with 4.4 parts by volume of triethylamine and 4.0 parts by weight of anhydrous sodium sulfate and then stirred for two hours at room temperature. After filtration, the solution was cooled to -20°C and combined with the mixture A. The reaction mixture was left to reach 0°C of its own accord, and was then stirred for a further hour at 0°C. The solvent was removed in a rotary evaporator, the residue was dissolved in water, and the solution was covered with a layer of ethyl acetate and acidified with dilute hydrochloric acid at 0° to 5°C, while stirring, until pH 1.5 was reached. The organic phase was then separated off, washed with water, dried over magnesium sulfate while cooling, and filtered, and after dilution with an equal amount of ether the sodium salt of the penicillin was precipitated from the filtrate by adding a solution of sodium 2-ethylcaproate dissolved in ether containing methanol. Yield: 1.3 parts by weight.

References

Merck Index 916
Kleeman & Engel p. 69
PDR p. 1247
OCDS Vol. 3 p. 206 (1984)
DOT 13 (10) 409 (1977)
I.N. p. 111
REM p. 1200
Konig, H.B., Schrock, W., Disselknotter, H. and Metzger, K.G.; U.S. Patents 3,933,795; January 20, 1976; 3,936,442; February 3, 1976; 3,939,149; February 17, 1976; 3,974,140; August 10, 1976; 3,978,223; August 31, 1976 and 3,980,792; September 14, 1976; all assigned to Bayer AG

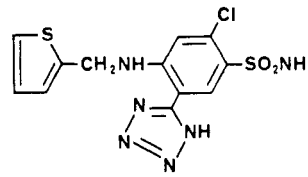
AZOSEMIDE

Therapeutic Function: Diuretic

Chemical Name: 5-(4'-Chloro-2'-thenylamino-5'-sulfamoylphenyl)tetrazole

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 27589-33-9

Trade Name	Manufacturer	Country	Year Introduced
Diurapid	Boehringer-Mann	W. Germany	1981

Raw Materials

4-Chloro-2-fluoro-5-sulfamoyl Benzonitrile
Thenylamine
Sodium Azide

Manufacturing Process

The 4-chloro-5-sulfamoyl-2-thenylamino-benzonitrile used as starting material is obtained by the reaction of 4-chloro-2-fluoro-5-sulfamoyl-benzonitrile with thenylamine in anhydrous tetrahydrofuran.

Then the 5-(4'-chloro-5'-sulfamoyl-2'-thenylamino)phenyltetrazole (MP 218° to 221°C; yield 37% of theory) is obtained by the reaction of 4-chloro-5-sulfamoyl-2-thenylaminobenzonitrile (MP 170° to 174°C) with sodium azide and ammonium chloride.

References

Merck Index 922
DFU 4 (6) 393 (1979)
OCDS Vol. 3 p. 27 (1984)
Popelek, A., Lerch, A., Stach, K., Roesch, E. and Hardebeck, K.; U.S. Patent 3,665,002; May 23, 1972; assigned to Boehringer Mannheim GmbH