A

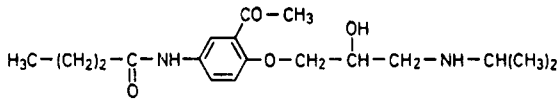
ACEBUTOLOL

Therapeutic Function: Cardiovascular beta-blocker

Chemical Name: N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)-amino] propoxy] phenyl] butanamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 37517-30-9; 34381-68-5 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Sectral	May & Baker	UK	1975
Sectral,	Specia	France	1976
Prent	Bayer	W. Germany	1977
Neptall	Rhodia Pharma	W. Germany	1977
Sectral	May & Baker	Switzerland	1980
Sectral	Roger Bellon	Italy	1980
Sectral	RBJ Pharma	Italy	1980
Acetanol	Kanebo	Japan	1981
Prent	Bayer	Italy	1981
Acecor	S.P.A.	Italy	–
Diasectral	Rhone Poulenc	–	–
Neptal	Rohm Pharma	–	–
Secradex	May & Baker	U.K.	–
Sectral	Wyeth	U.S.	–

Raw Materials

Butyramidophenol
Acetyl Chloride
Aluminum Chloride
Epichlorohydrin
Sodium Ethoxide
Isopropylamine

Manufacturing Process

Crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone (16 g), isopropylamine (20 g) and ethanol (100 ml) were heated together under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure and the residual oil was dissolved in N hydrochloric acid. The acid solution was extracted with ethyl acetate, the ethyl acetate layers being discarded. The acidic solution was brought to pH 11 with 2 N aqueous sodium hydroxide solution and then extracted with chloroform. The dried chloroform extracts were concentrated under re-

duced pressure to give an oil which was crystallized from a mixture of ethanol and diethyl ether to give 5'-butyramido-2'-(2-hydroxy-3-isopropylaminopropoxy)acetophenone (3 g), MP 119°–123°C.

Crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone used as starting material was prepared as follows: p-butyramidophenol (58 g; prepared according to Fierz-David and Kuster, Helv. Chim. Acta 1939, 2282), acetyl chloride (25.4 g) and benzene (500 ml) were heated together under reflux until a solution formed (12 hours). This solution was cooled and treated with water. The benzene layer was separated and the aqueous layer was again extracted with benzene.

The combined benzene extracts were dried and evaporated to dryness under reduced pressure to give p-butyramidophenyl acetate (38 g) as an off-white solid, MP 102°–103°C. A mixture of p-butyramidophenyl acetate (38 g), aluminum chloride (80 g) and 1,1,2,2-tetrachloroethane (250 ml) was heated at 140°C for 3 hours. The reaction mixture was cooled and treated with iced water. The tetrachloroethane layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were extracted with 2N aqueous sodium hydroxide and the alkaline solution was acidified to pH 5 with concentrated hydrochloric acid. The acidified solution was extracted with chloroform and the chloroform extract was dried and concentrated under reduced pressure to give 5'-butyramido-2'-hydroxyacetophenone (15.6 g), MP 114°–117°C. A solution of 5'-butyramido-2'-hydroxyacetophenone (15.6 g) in ethanol (100 ml) was added to an ethanolic solution of sodium ethoxide which was prepared from sodium (1.62 g) and ethanol (100 ml). The resulting solution was evaporated to dryness under reduced pressure and dimethylformamide (100 ml) was added to the solid residue. Approximately 10 ml of dimethylformamide was removed by distillation under reduced pressure. Epichlorohydrin (25 ml) was added and the solution was heated at 100°C for 4 hours. The solution was concentrated under reduced pressure to give a residual oil which was treated with water to give a solid. The solid was dissolved in ethanol and the resulting solution was treated with charcoal, filtered and concentrated under reduced pressure to give crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone (16 g), MP 110°–116°C.

The crude compound may be purified by recrystallization from ethyl acetate, after treatment with decolourizing charcoal, to give pure 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone, MP 136°–138°C.

References

Merck Index 13
Kleeman & Engel p. 1
PDR p. 1978
OCDS Vol. 2 p. 109 (1980)
DOT 11 (7) p. 264 (1975)
I.N. p. 2
Wooldridge, K.R.H. and Basil, B.; U.S. Patent 3,857,952; Dec. 31, 1974; assigned to May & Baker, Ltd.

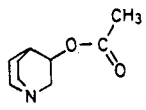
ACECLIDINE

Therapeutic Function: Miotic, cholinomimetic

Chemical Name: 1-Azabicyclo[2.2.2] octan-3-ol acetate

Common Name: 3-Quinuclidinol Acetate

Structural Formula:



Chemical Abstracts Registry No.: 827-61-2; 6109-70-2 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Glacostat	MSD-Chibret	France	1966
Glaunorm	Farmigea	Italy	1969
Glaudin	SIFI	Italy	—

Raw Materials

Methyl Isonicotinate
Ethyl Bromoacetate
Potassium Metal
Hydrogen

Manufacturing Process

A mixture of 274 g of methyl isonicotinate, 367 g of ethyl bromoacetate and 125 cc of ethyl alcohol was stirred without heating for 4 hours in a flask equipped with a reflux condenser. (The reaction was exothermic and precautions were taken to keep the temperature below 70°C.) The reaction mixture was then left for 15 hours at room temperature.

The reaction product (1-carbethoxymethyl-4-carbomethoxy-pyridinium bromide) was obtained in crystalline form. (It formed prisms melting at 166°-169°C after recrystallization from a mixture of isopropanol and acetone.) It was not necessary to isolate it. For the following reduction step, the reaction mixture was brought into solution by the addition of about 1 liter of warm ethyl alcohol. It was then hydrogenated at about 30 atm pressure in the presence of 2 g of platinum oxide. The temperature rose during this reaction to about 40°C. After the calculated amount of hydrogen had been absorbed, the catalyst was filtered off, the solution was concentrated in vacuo, and the residual syrup was dissolved in ice water. Benzene was added and the mixture was made alkaline with an excess of concentrated ice cold potassium carbonate solution. The temperature was kept low by continuous addition of ice, and the benzene layer was separated and dried with sodium sulfate. The dried benzene solution was concentrated in vacuo and the residual oil was distilled in vacuo. BP 30 mm = 175°-182°C, n_D^{25} = 1.4613-1.4628. During the reduction, partial alcoholysis occurred, and the product isolated was 1-carbethoxymethyl-4-"carbalkoxy"-piperidine, wherein "carbalkoxy" represents a mixture of carbomethoxy and carbethoxy.

100 g of potassium were pulverized in 200 cc of hot toluene in a heated three-neck flask equipped with an efficient condenser, stirrer and dropping funnel. To the refluxing potassium suspension were added in small portions 229 g of the product of the previous step and about 700 cc of toluene. This addition had to be carried out very cautiously; the onset of the exothermic reaction is sometimes delayed. The addition was finished in about 1 hour. To complete the reaction, the refluxing and stirring were continued for about 4 hours. The reaction mixture was then cooled to about +5°C and about 50 cc isopropanol were added to decompose unreacted potassium. Then 2.5 liters of concentrated hydrochloric acid were added and the mixture was refluxed for 15 hours, and then concentrated in vacuo to dryness. To the residue was added with cooling an excess of 50% potassium hydroxide. Ether was then added and the resulting mixture was filtered through a fritted glass funnel, thus removing the precipitated potassium chloride. The ethereal and aqueous layers were separated, and the aqueous layer was extracted repeatedly with 500 cc portions of ether. The organic solutions were combined, dried over sodium sulfate and concentrated in vacuo. Aqueous hydrochloric acid was added to the residue until the solution became acid. The mixture was then diluted with distilled water to about 300 cc, heated with decolorizing charcoal, filtered and concentrated in vacuo to dryness. The residue was treated with isopropanol, and the precipitated crystalline product was filtered off. The product was recrystallized from a mixture of water and isopropanol and was

identified as 1-azabicyclo[2.2.2]-3-octanone hydrochloride; prisms, MP 311°–313°C, with decomposition.

A solution of 50 g of the above ketone-hydrochloride in 30 cc of water was made alkaline by the addition of 30 g of potassium hydroxide. After the alkali was dissolved, 35 g of granular potassium carbonate were added. The free basic ketone was then extracted from the viscous mixture by shaking with 4 portions of hot benzene (300 cc in each portion). The benzene extracts were decanted, filtered over sodium sulfate in order to remove any suspended alkali, and concentrated in vacuo. The residual 1-azabicyclo[2.2.2]-3-octanone was purified by sublimation (50°–70°C/0.5 mm Hg); it can also be purified by recrystallization from petroleum ether. It formed feathery crystals melting at 147°–148°C.

The product was reduced as follows:

A solution of 50 g of 1-azabicyclo[2.2.2]-3-octanone hydrochloride in 200 cc of water was hydrogenated at room temperature and 50 atm pressure with 1 g of platinum oxide as catalyst. After the calculated amount of hydrogen had been absorbed, the mixture was filtered and concentrated in vacuo to dryness. The residual product was recrystallized from a mixture of methanol and acetone and formed prisms melting above 300°C. It was identified as 1-azabicyclo[2.2.2]-3-octanol hydrochloride.

A solution of 50 g of 1-azabicyclo[2.2.2]-3-octanol hydrochloride in 30 cc water was made alkaline with 30 g of potassium hydroxide. After the alkali was dissolved 35 g of granular potassium carbonate were added. The free basic alcohol was then extracted from the viscous mixture by shaking with four portions of boiling benzene (300 cc in each portion). The benzene extracts were decanted and filtered over anhydrous sodium sulfate, to remove any suspended alkali. The combined benzene solutions were concentrated in vacuo. The residue was recrystallized from benzene and identified as 1-azabicyclo[2.2.2]-3-octanol, MP 221°–223°C. The product can also be purified by recrystallization from acetone, or by sublimation in vacuo (120°C/20 mm Hg). The alcohol was reacted with acetic anhydride to give the product aceclidine.

References

Kleeman & Engel p. 2
OCDS Vol. 2 p. 295 (1980)
I.N. p. 2
Sternbach, L.H.; U.S. Patent 2,648,667; Aug. 11, 1953; assigned to Hoffman-La Roche Inc.

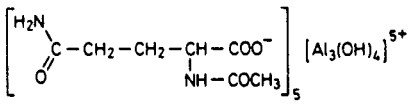
ACEGLUTAMIDE ALUMINUM

Therapeutic Function: Antiulcer (free base as psychostimulant)

Chemical Name: Pentakis(N^2-acetyl-L-glutaminato)tetrahydroxytrialuminum

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 12607-92-0

Trade Name	Manufacturer	Country	Year Introduced
Glumal	Kyowa Hakko	Japan	1978
Glumal	Liade	Spain	–

Raw Materials

N-Acetyl-L-Glutamine
Aluminum Isopropoxide

Manufacturing Process

A mixture of 37.6 g of N-acetyl-L-glutamine and 1,000 ml of water is heated to 40°C, and 900 ml of an isopropanol solution containing 40.8 g of aluminum isopropoxide is added to the warm mixture with stirring. The stirring is continued for 10 minutes. The reaction mixture is filtered and the filtrate is concentrated under reduced pressure. Isopropanol is added to the aqueous solution and the salt precipitates in the solution. The precipitates are collected by filtration and upon drying, 48.5 g of the crystalline-like aluminum salt of N-acetyl-L-glutamine are obtained.

References

Merck Index 20
Kleeman & Engel p. 32
DOT 14 (2) p. 54 (1978)
I.N. p. 3
Kagawa, T., Fuji, K., Tanaka, M. and Tanaka, H.; U.S. Patent 3,787,466; Jan. 22, 1974; assigned to Kyowa Hakko Kogyo Co., Ltd.

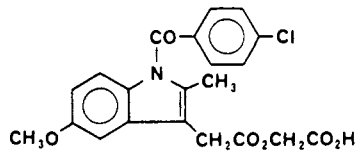
ACEMETACIN

Therapeutic Function: Antiinflammatory

Chemical Name: 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetoxyacetic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53164-05-9

Trade Name	Manufacturer	Country	Year Introduced
Rantudil	Bayer	W. Germany	1980
Rantudil	Tropon	W. Germany	–

Raw Materials

N-(p-Methoxybenzyl)-p-Chlorobenzhydrazide HCl
Benzyl Levulinoyloxyacetate
Hydrogen

Manufacturing Process

25.4 g (0.050 mol) of [1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetoxy]-benzyl acetate were dissolved in 400 ml of glacial acetic acid and hydrogenated on 2.0 g of palladium carbon at room temperature. After the absorption of hydrogen had finished (1 hour), the catalyst was filtered off, the filtrate was concentrated by evaporation under vacuum and the compound was caused to crystallize by adding petroleum ether. The compound melted at 149.5°-150.5°C (determined on the micro-Kofler bench); the yield was 19.4 g which corresponds to 93% of the theoretical yield.

The starting material for the above step may be prepared as follows: 5 g (0.016 mol) of N^1-(p-methoxyphenyl)-p-chlorobenzhydrazide hydrochloride and 4.75 g (0.018 mol) of benzyl levulinoyloxyacetate were heated in 25 ml of glacial acetic acid for 3 hours at 80°C. The solvent was then evaporated off under vacuum. The residue was taken up in chloroform and the solution was washed neutral by shaking with sodium bicarbonate solution and thereafter with water. After drying the chloroform solution, this was subjected to chromatography on aluminium oxide, the eluate was concentrated by evaporation and the viscous oil remaining as residue was crystallized by adding ether. The compound melted at 94°-95°C. The yield was 4.1 g which corresponds to 50.7% of the theoretical yield.

References

Merck Index 21
DFU 2 (7) p. 423 (1977)
Kleeman & Engel p. 3
DOT 17 (7) p. 279 (1981)
I.N. p. 3
Boltze, K.H., Brendler, O., Dell, H.D. and Jacobi, H.; U.S. Patent 3,910,952; October 7, 1945; assigned to Tropenwerke Dinklage and Co.
Boltze, K.H., Brendler, O., Dell, H.D. and Jacobi, H.; U.S. Patent 3,966,956; June 29, 1976; assigned to Tropenwerke Dinklage and Co.

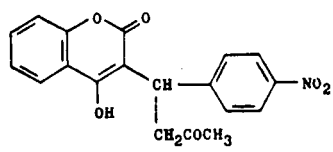
ACENOCOUMAROL (ACENOCOUMARIN)

Therapeutic Function: Anticoagulant, Vitamin K antagonist

Chemical Name: 3-(α-acetonyl-p-nitrobenzyl)-4-hydroxycoumarin

Common Name: Nicoumalone

Structural Formula:



Chemical Abstracts Registry No.: 152-72-7

Trade Name	Manufacturer	Country	Year Introduced
Sintrom	Geigy	U.S.	1957
Sintrom	Geigy	W. Germany	—
Sintrom	Ciba Geigy	Switz.	—
Sintrom	Ciba-Geigy	France	1959

Trade Name	Manufacturer	Country	Year Introduced
Neo-Sintrom	Geigy	–	–
Ascumar	Star	Finland	–
Syncumar	Egyt	Hungary	–
Synthrome	Geigy	U.K.	–
Sintrom	Ciba-Geigy-Fujisawa	Japan	–

Raw Materials

4-Hydroxycoumarin
Nitrobenzalacetone

Manufacturing Process

16 parts of 4-hydroxycoumarin and 19 parts of 4-nitrobenzalacetone are thoroughly mixed and heated for 12-14 hours in an oil bath, the temperature of which is between 135° and 140°C. After cooling, the melt is dissolved in a little acetone. The solution is slowly added to a lye made up from 6 parts of sodium hydroxide in 400 parts of water while stirring and then the mixture is stirred for 30 minutes. A little animal charcoal is then added, the mixture is stirred for a further 15 minutes, 400 parts of water are added and the charcoal and undissolved components are separated by filtration under suction. The clear solution is made acid to Congo red paper with hydrochloric acid and the product which is precipitated is filtered off under suction. 3-[α-(4'-nitrophenyl)-β-acetyl ethyl]-4-hydroxycoumarin is obtained. MP 196°-199°C.

It should be noted that the process is akin to that for Warfarin except that 4-nitrobenzalacetone replaces benzalacetone as a raw material.

References

Merck Index 23
Kleeman & Engel p. 4
OCDS Vol. 1 p. 331 (1977)
I.N. p. 3
Stoll, W. and Litvan, F.; U.S. Patent 2,648,682; August 11, 1953; assigned to J.R. Geigy A.G., Switzerland.

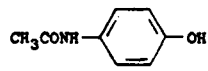
ACETAMINOPHEN

Therapeutic Function: Analgesic, antipyretic

Chemical Name: N-(4-hydroxyphenyl)acetamide

Common Name: Paracetamol, Acetyl-p-Aminophenol, APAP

Structural Formula:



Chemical Abstracts Registry No.: 103-90-2

Trade Name	Manufacturer	Country	Year Introduced
–	–	Germany	1878

Trade Name	Manufacturer	Country	Year Introduced
Trigesic	Squibb	U.S.	1950
Apamide	Ames (Dome)	U.S.	1952
Nebs	Norwich (Eaton)	U.S.	1955
Tylenol	McNeil	U.S.	1955
Febrolin	Tilden Yates	U.S.	1957
Tempra	Mead Johnson	U.S.	1957
Fendon	Am. Pharm.	U.S.	1958
Amdil	Breon	U.S.	1958
Lyteca	Westerfield	U.S.	1962
Menalgesia	Clapp	U.S.	1963
Dial-Agesic	Borden	U.S.	1968
Tenlap	Dow	U.S.	1970
SK-APAP	SK&F	U.S.	1971
Valadol Tablets	Squibb	U.S.	1971
Tapar	Parke-Davis	U.S.	1974
Cen-Apap	Central	U.S.	1974
Acephen	G&W	U.S.	1978
St. Joseph Aspirin	St. Joseph	U.S.	1982
Panadol	Glenbrook	U.S.	1983
Pain & Fever	Lederle	U.S.	1983
Accu-Tap	Accu-Med	U.S.	–
Actamin	Buffington	U.S.	–
Aminofen	Dover	U.S.	–
Anuphen	Comatic	U.S.	–
Dapa	Ferndale	U.S.	–
Datril	Bristol-Myers	U.S.	–
Dirox	Winthrop	U.S.	–
Dolanex	Lannett	U.S.	–
Febrogesic	First Texas	U.S.	–
Halenol	Halsey	U.S.	–
Hedex	Winthrop	U.S.	–
Homoolan	Winthrop	U.S.	–
Injectapap	Johnson & Johnson	U.S.	–
Korum	Geneva	U.S.	–
Metalid	Philips-Roxane	U.S.	–
Minotal	Carnrick	U.S.	–
Neopap	Webcon	U.S.	–
Neotrend	Bristol-Myers	U.S.	–
Nilprin	AVP	U.S.	–
Panamax	Winthrop	U.S.	–
Panodil	Winthrop	U.S.	–
Parten	Parmed	U.S.	–
Phenaphen	Robins	U.S.	–
Phendex	Mallard	U.S.	–
Phrenilin	Carnrick	U.S.	–
Prompt	Delree	U.S.	–
Proval	Reid-Provident	U.S.	–
Robigesic	Robins	U.S.	–
Valorin	Otis Clapp	U.S.	–
Abrol	Rekah	Israel	–
Abrolet	Rekah	Israel	–
Acamol	Ikapharm	Israel	–
Acetalgin	Streuli	Switz.	–
Aldolor	Novis	Israel	–
Alpiny	SS Pharmaceut.	Japan	–
Alvedon	Draco	Sweden	–

Trade Name	Manufacturer	Country	Year Introduced
Anaflon	Duphar	U.K.	–
Anhiba	Hokuriku	Japan	–
APA/Aparacet	Arcana	Austria	–
Apiretal	Ern	Spain	–
Arasol	Horner	Canada	–
Benmyo	Heilmittelwerke	Austria	–
Ben-U-Ron	Benechemie	W. Germany	–
Calpol	Calmic	U.K.	–
Campain	Winthrop	Canada	–
Ceetamol	Protea	Australia	–
Cetadol	Rybar	U.K.	–
Chemcetaphen	Chemo-Drug	Canada	–
Dipramat Infantil	Byk-Gulden	W. Germany	–
Dolamin	Nyal	Australia	–
Doliprane	Bottu	France	–
Dolprone	Siegfried	W. Germany	–
Dymadon	Calmic	U.K.	–
Efferalgan	UPSA	France	–
Enelfa	Dolorgiet	W. Germany	–
Exdol	Merck-Frosst	Canada	–
Febrilix	Boots	U.K.	–
Finimal	Mepros	Neth.	–
Finimal	Pharmaton	Switz.	–
Gelocatil	Gelos	Spain	–
Ildamol	Rekah	Israel	–
Kinder-Finiweh	Cesmopharma	Neth.	–
Kratofin	Kwizda	Austria	–
Labamol	Vitamed	Israel	–
Langesic	Boots	U.K.	–
Letamol	Letap	Switz.	–
Momentum	Much	W. Germany	–
Myalgin	Allied Labs	U.K.	–
Napional	Pharma Import	Austria	–
Nealgyl	Bottu	France	–
Nevral	Lepetit	Italy	–
Pacemo	Alpinapharm	Switz.	–
Pacet	Rekah	Israel	–
Painex	A.L.	Norway	–
Pamol	Marshalls Pharm.	U.K.	–
Panacete	Prosana	Australia	–
Panadol	Sterwin-Espanola	Spain	–
Panadon	Isis	Yugoslavia	–
Panasorb	Winthrop	U.K.	–
Panasorb	Bayer	W. Germany	–
Panok	B.M. Labs	U.K.	–
Pantalgin	UCB	Belgium	–
Paracet	Zdravlje	Yugoslavia	–
Paracet	Weifa	Norway	–
Paralgin	ICN	Canada	–
Paramol	Duncan Flockhart	U.K.	–
Paramolan	Trima	Israel	–
Parasin	Adams	Australia	–
Paraspen	Fisons	U.K.	–
Para-Suppo	Orion	Finland	–
Parmol	Knoll	Australia	–
Parol	Atabay	Turkey	–
Pasolind	Stada	W. Germany	–

Trade Name	Manufacturer	Country	Year Introduced
PCM	Napp	U.K.	–
Pediaphen	Ross	Canada	–
Phenipirin	Aksu	Turkey	–
Pinex	A.L.	Norway	–
Puernol	Formenti	Italy	–
Pyrinazin	Yamanouchi	Japan	–
Pyrital	Medica	Finland	–
Reliv	ACO	Sweden	–
Rivalgyl	Rivopharm	Switz.	–
Rounox	Rougier	Canada	–
Servigesic	Servipharm	Switz.	–
Setamol	Pharmacia	Sweden	–
Setol	Dif-Dogu	Turkey	–
Supramol	Sam-On	Israel	–
Tabalgin	Bayer	W. Germany	–
Tachipirina	Angelini	Italy	–
Temperal	Prodes	Spain	–
Trenodin	Fresenius	W. Germany	–
Tymol	Reckitt & Colman	W. Germany	–
Veralydon	Lelong	France	–

Raw Materials

Nitrobenzene
Acetic Anhydride

Manufacturing Process

About 250 ml of a reaction mixture obtained by the electrolytic reduction of nitrobenzene in sulfuric acid solution and containing about 23 grams of p-aminophenol by assay is neutralized while at a temperature of 60° to 65°C, to a pH of 4.5 with calcium carbonate. The calcium sulfate precipitate which forms is filtered off, the precipitate washed with hot water at about 65°C and the filtrate and wash water then combined. The solution is then extracted twice with 25 ml portions of benzene and the aqueous phase is treated with 0.5 part by weight, for each part of p-aminophenol present, of activated carbon and the latter filtered off. The activated carbon is regenerated by treatment with hot dilute caustic followed by a hot dilute acid wash, and reused a minimum of three times.

To the filtrate obtained, there are then added about 0.2 gram of sodium hydrosulfite or sodium sulfite and 15.0 grams of anhydrous sodium acetate in about 27 grams of acetic anhydride at 40°C. The reaction mixture formed is cooled to 8° to 10°C with stirring and held at this temperature for 60 minutes. A crystalline precipitate of about 27 grams of N-acetyl-p-aminophenol is obtained melting at 169°-171°C. This is equivalent to a yield of 85%.

In lieu of utilizing calcium carbonate as the neutralizing agent, calcium hydroxide, barium hydroxide, barium chloride or other alkaline earth metal salt or hydroxide forming an insoluble sulfate may be employed.

References

Merck Index 39
Kleeman & Engel p. 684
PDR p. Many References
OCDS Vol. 1 p. 111 (1977)
DOT 16 (2) p. 59 (1980)
I.N. p. 728
REM p. 1111

Wilbert, G. and De Angelis, J.; U.S. Patent 2,998,450; August 29, 1961; assigned to Warner-Lambert Pharmaceutical Company.

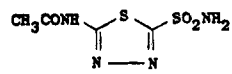
ACETAZOLAMIDE

Therapeutic Function: Carbonic anhydrase inhibitor, diuretic, treatment of glaucoma

Chemical Name: N-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl] acetamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 59-66-5

Trade Name	Manufacturer	Country	Year Introduced
Diamox	Lederle	U.S.	1953
Hydrazole	Softcon Products	U.S.	1975
Acetamide	Nessa	Spain	–
Acetamox	Santen	Japan	–
Acetazolam	ICN	Canada	–
Acetazolamide Chibret	Chibret	France	–
Albox	Kwizda	Austria	–
Atenezol	Tsuruhara	Japan	–
Defiltran	Jouveinal	France	–
Diazomid	Dif-Dogu	Turkey	–
Diamox	Theraplix	France	–
Didoc	Sawai	Japan	–
Diluran	Spofa	Czech.	–
Diuramid	Polfa	Poland	–
Dirureticum-Holzinger	Holzinger	Austria	–
Diuriwas	Wassermann	Italy	–
Donmox	Hotta	Japan	–
Edemox	Wassermann	Spain	–
Glauconox	Llorens	Spain	–
Glaupax	Erco	Denmark	–
Glaupax	Baeschlin	W. Germany	–
Glaupax	Dispersa	Switz.	–
Inidrase	Omikron-Gagliardi	Italy	–
Nephramid	Chemiek	E. Germany	–
Oedemin	Astra	Sweden	–
Renamid	Pliva	Yugoslavia	–
Uramox	Taro	Israel	–
Zohnox	Konto	Japan	–

Raw Materials

Hydrazine Hydrate
Ammonium Thiocyanate
Acetic Anhydride
Chlorine
Ammonia
Bromine

Manufacturing Process

According to REM, hydrazine hydrate is reacted with 2 mols of ammonium thiocyanate to produce 1,2-bis(thiocarbamoyl)hydrazine which by loss of ammonia and rearrangement produces 5-amino-2-mercapto-1,3,4-thiadiazole. That compound is acetyled with acetic anhydride.

Then, as described in U.S. Patent 2,554,816, the 2-acetylamido-5-mercapto-1,3,4-thiadiazole is converted to the sulfonyl chloride by passing chlorine gas into a cooled (5°–10°C) solution in 33% acetic acid (66 parts to 4 parts of mercapto compound) used as a reaction medium. Chlorine treatment is continued for two hours. The crude product can be dried and purified by recrystallization from ethylene chloride. The pure compound is a white crystalline solid, MP 194°C, with decomposition, when heated rapidly. The crude damp sulfonyl chloride is converted to the sulfonamide by addition to a large excess of liquid ammonia. The product is purified by recrystallization from water. The pure compound is a white, crystalline solid, MP 259°C, with decomposition. The yield of sulfonamide was 85% of theory based on mercapto compound.

An alternative process is described in U.S. Patent 2,980,679 as follows. 15 grams of finely powdered 2-acetylamino-1,3,4-thiadiazole-5-mercaptain are suspended in 200 ml of water containing 4 grams of potassium bromide. From 0.5 to 1 gram of ferric chloride are subsequently added. The mass is energetically stirred and 52 grams of liquid bromide are added by increments for about 45 minutes, while keeping the reaction temperature below 10°C, and, preferably, at 4°–8°C by employing a cooling bath. Stirring is continued for a further 10 minutes, then the 2-acetylamino-1,3,4-thiadiazole-5-sulfobromide is collected on a funnel equipped with a porous diaphragm, thoroughly washed with cold water and finally subjected to amidation with liquid ammonia. The reaction mixture is allowed to stand for a certain period, then the ammonia is evaporated, after which the residue is taken up with diluted ammonia and, after decolorizing with carbon, the sulfonamide is precipitated with hydrochloric acid. The yield of crude sulfonamide obtained with this process, with respect to the starting mercapto compound is about 84%. If the amidation is carried out with 33% aqueous ammonia, the yield is slightly lower.

References

Merck Index 45
Kleeman & Engel p. 6
PDR pp. 830, 1008, 1606
OCDS Vol 1 p. 249 (1977)
I.N. p. 5
REM p. 936
Clapp, J.W. and Roblin, R.O., Jr.; U.S. Patent 2,554,816; May 29, 1951; assigned to Americar Cyanamid Company.
Gianfranco, P.; U.S. Patent 2,980,679; April 18, 1961; assigned to Omikron-Gagliardi Societa di Fatto, Italy.

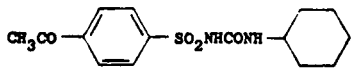
ACETOHEXAMIDE

Therapeutic Function: Hypoglycemic

Chemical Name: 1-[(p-acetylphenyl)sulfonyl]-3-cyclohexylurea

Common Name: Cyclamide

Structural Formula:



Chemical Abstracts Registry No.: 968-81-0

Trade Name	Manufacturer	Country	Year Introduced
Dymelor	Lilly	U.S.	1964
Dimelin	Shionogi	Japan	–
Dimelor	Lilly	U.K.	–
Gamadiabet	Salvat	Spain	–
Metaglucina	Perga	Span	–
Ordimel	Lilly	Spain	–

Raw Materials

p-Aminoacetophenone
Sodium Nitrite
Hydrogen Chloride
Sulfur Dioxide
Ammonia
Cyclohexyl Isocyanate

Manufacturing Process

Preparation of p-Acetylbenzenesulfonamide: 100 grams of p-aminoacetophenone were dissolved in a solvent mixture containing 165 ml of 12 N hydrochloric acid and 165 ml of glacial acetic acid. The mixture was cooled with stirring to about 0°C. A solution containing 56.2 grams of sodium nitrite and 175 ml of water was added dropwise with stirring to the acidic solution while maintaining the temperature below 5°C.

After the addition had been completed, the acidic solution containing p-acetylphenyldiazonium chloride formed in the above reaction was added dropwise with stirring to a mixture of 530 ml of glacial acetic acid and 530 ml of benzene which had been previously cooled, and the cooled solution saturated with sulfur dioxide and to which had been added 34 g of cupric chloride dihydrate. After the addition had been completed, the reaction mixture was stirred at about 40°C for three hours, and was then poured into 3,000 ml of an ice-water mixture.

The benzene layer containing p-acetylbenzenesulfonyl chloride formed in the above reaction was separated, and the acidic aqueous phase was extracted twice with 250 ml portions of benzene. The benzene layers were combined, the combined extracts were filtered, and the benzene was evaporated from the resulting filtrate in vacuo.

The solid residue comprising p-acetylbenzenesulfonyl chloride was dissolved in 100 ml of dioxane, and the solution was added to 200 ml of 14% aqueous ammonium hydroxide. The resulting solution was stirred overnight at ambient room temperature. The p-acetylbenzenesulfonamide thus prepared was collected by filtration. Recrystallization of the filter cake from aqueous ethanol yielded purified p-acetylbenzenesulfonamide melting at about 176° to 179°C.

Preparation of N-p-Acetylphenylsulfonyl-N'-Cyclohexylurea: A reaction mixture consisting of 32.7 grams of p-acetylbenzenesulfonamide and 64 grams of anhydrous potassium carbonate in 350 ml of anhydrous acetone was stirred at refluxing temperature for about 1½ hours, thus forming the potassium salt of p-acetylbenzenesulfonamide. 30.9 grams of cyclohexylisocyanate were added dropwise to the reaction mixture. Refluxing and stirring were continued during the course of the addition and for an additional 16 hours.

The acetone was removed by evaporation in vacuo, and about 750 ml of water were added to dissolve the resulting residue. The solution was filtered. The potassium salt of N-p-acetylphenylsulfonyl-N'-cyclohexylurea formed in the above reaction, being water-soluble, passed into the filtrate. Acidification of the filtrate with 6 N aqueous hydrochloric acid caused the precipitation of N-p-acetylphenylsulfonyl-N'-cyclohexylurea which was collected by filtration. Recrystallization of the filter cake from 90% aqueous ethanol yielded purified N-p-acetylphenylsulfonyl-N'-cyclohexylurea melting at about 188°-190°C.

References

Merck Index 53
Kleeman & Engel p. 7
PDR p. 1049
OCDS Vol. 1 p. 138 (1977)
I.N. p. 6
REM p. 976
Sigal, M.V., Jr. and Van Arendonk, A.M.; U.S. Patent 3,320,312; May 16, 1967; assigned to Eli Lilly and Company.

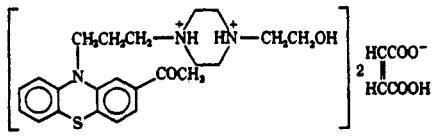
ACETOPHENAZINE DIMALEATE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[3-[4-(2-hydroxyethyl)-1-piperazinyl] propyl] phenothiazin-2-yl methyl ketone maleate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 5714-00-1; 2751-68-0 (Acetophenazine)

Trade Name	Manufacturer	Country	Year Introduced
Tindal	Schering	U.S.	1961

Raw Materials

Sodium Amide
2-Acetylphenothiazine
1-Bromo-3-Chloropropane
1-(2-Hydroxyethyl)piperazine
Maleic Acid

Manufacturing Process

The requisite intermediate, 10-(3-chloropropyl)-2-acetylphenothiazine is prepared as follows: To a suspension of sodamide (from 3 grams of sodium) in 300 ml of liquid ammonia is added 30 grams of 2-acetylphenothiazine. After stirring for one hour, there is added 19 grams of 1-bromo-3-chloropropane. The ammonia is allowed to evaporate and the residue is diluted with 200 ml of water. The mixture is extracted with ether and the ether solution is dried over anhydrous sodium sulfate, filtered and concentrated.

The residue consists of crude 10-(3-chloropropyl)-2-acetylphenothiazine as a viscous oil and is used in the next step without further purification. The crude base obtained from the reaction of 10-(3-chloropropyl)-2-acetylphenothiazine with 1-(2-hydroxyethyl)piperazine is purified by conversion to its dimaleate salt, MP 167°-168.5° from ethanol.

References

Merck Index 64
Kleeman & Engel p. 7

OCDS Vol. 1 p. 383 (1977)
I.N. p. 6
REM p. 1086
Sherlock, M.H. and Sperber, N.; U.S. Patent 2,985,654; May 23, 1961; assigned to Schering Corporation.

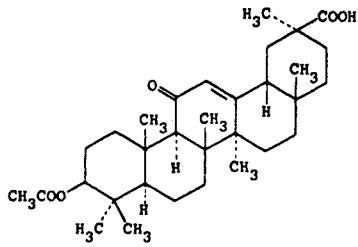
ACETOXOLONE ALUMINUM SALT

Therapeutic Function: Antiulcerative

Chemical Name: 3-(acetyloxy)-11-oxoolean-12-en-29-oic acid aluminum salt

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 6277-14-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Oriens	Inverni Beffa	Italy	1981

Raw Materials

3-Acetyl-18β-glycerrhetinic Acid
Aluminum Alcoholate

Manufacturing Process

The salts of 3-acetyl-18β-glycyrrhetinic acid can be prepared by reaction between 3-acetyl-18β-glycyrrhetinic acid and an aluminum alcoholate. Preferably lower alcoholates are used, i.e., alcoholates in which the alkoxy group or groups have from one to four carbon atoms. The salification reaction may be carried out at room temperature or at an elevated temperature in conventional fashion, preferably in the presence of organic solvents. As organic solvents may be used alcohols, ethers, ketones, chlorinated solvents (methylene chloride, chloroform) ethyl acetate, etc.

References

Merck Index 70
Bonati, A.; U.S. Patent 3,764,618; October 9, 1973; assigned to Dott. Inverni & Della Befia S.p.A.

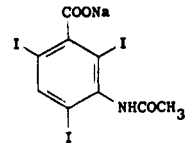
ACETRIZOATE SODIUM

Therapeutic Function: X-ray contrast medium

Chemical Name: 3-(Acetylamino)-2,4,6-triiodobenzoic acid sodium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 129-63-5

Trade Name	Manufacturer	Country	Year Introduced
Urokon Sodium	Mallinckrodt	U.S.	1950
Thixokon	Mallinckrodt	U.S.	1957
Cystokon	Mallinckrodt	U.S.	1964
Pyelokon-R	Mallinckrodt	U.S.	–
Salpix	Ortho	U.S.	–
Diaginol	May & Baker	U.K.	–
Diaginol	Banyu	Japan	–
Vasurix	Guerbet	France	–
Fortombrin	Dagra	Neth.	–
Iodopaque	Labaz	Switz.	–
Triurol	Lundbeck	Denmark	–

Raw Materials

3-Amino-2,4,6-triiodobenzoic Acid
Acetic Anhydride
Sodium Hydroxide

Manufacturing Process

3-amino-2,4,6-triiodobenzoic acid (51.5 g) was mixed with 125 ml of acetic anhydride containing 2 drops of concentrated sulfuric acid and refluxed for thirty minutes. The mixture was allowed to cool slightly, and then was poured into 600 ml of water at room temperature and stirred until crystallization was complete. The mixed anhydride of 3-acetylamino-2,4,6-triiodobenzoic acid with acetic acid thus prepared was then separated by filtration and washed with water. Without drying, the solid was suspended in 600 ml of water and hydrolyzed with a slight excess of ammonium hydroxide. It was necessary to warm the mixture slightly and stir it for about one-half hour in order to dissolve all the solid. The solution was then treated with activated carbon, filtered and precipitated with an excess of hydrochloric acid, filtered, washed and dried at 70°C. The yield was 51.5 g of 3-acetylamino-2,4,6-triiodobenzoic acid which melted at 276.6°-278.2°C with decomposition when placed in the melting block at 260°C and heated at the rate of 3°C per minute. Due to decomposition, the melting point varied from about 269°-280°C, depending upon the rate of heating and other conditions.

3-acetylamino-2,4,6-triiodobenzoic acid (28 g) was dissolved in a little over 50 ml of 1 N sodium hydroxide in a round-bottom flask. The pH was adjusted to slightly over 7 and the solution was evaporated on a steam bath under reduced pressure. After the residue became solid, it was further dried overnight in a vacuum desiccator containing calcium chloride. The salt weighed 31.2 g, theory being 29.0 g, indicating that the product contains about 7% water

of crystallization when dried under these conditions. The finished salt was scraped from the flask and ground.

References

Merck Index 73
Kleeman & Engel p. 8
I.N. p.7
Wallingford, V.H.; U.S. Patent 2,611,786; September 23, 1952; assigned to Mallinckrodt Chemical Works.

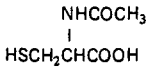
ACETYLCYSTEINE

Therapeutic Function: Expectorant

Chemical Name: N-acetyl-L-cysteine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 616-91-1

Trade Name	Manufacturer	Country	Year Introduced
Mucomyst	Mead Johnson	U.S.	1963
Acetein	Senju	Japan	—
Airbron	BDH	U.K.	—
Broncholysin	Spofa	Czech.	—
Brunac	Bruschettini	Italy	—
Fabrol	Ciba	—	—
Fluimucetin	Zambon	Italy	—
Fluimucetin	Inpharzam	Belgium	—
Fluimucil	Zambon	Italy	—
Inspir	Vitrum	Sweden	—
Mucolyticum	Lappe	W. Germany	—
Mucosolvin	VEB Berlin-Chemie	E. Germany	—
NAC	Mead Johnson	—	—
Parvolex	Duncan Flockhart	U.K.	—
Mucomist	Bristol	Italy	—
Mucisol	Deca	Italy	—
Rinofluimucil	Inpharzam	W. Germany	—
A.R.B.	Tokyo Tanabe	Japan	—
Mucofilin	Eisai	Japan	—

Raw Materials

L-Cysteine HCl
Acetic Anhydride

Manufacturing Process

To a suspension of 35.2 grams (0.2 mol) of L-cysteine hydrochloride monohydrate stirred in a reaction vessel containing 87 ml of 91% aqueous tetrahydrofuran under a nitrogen

atmosphere there is added 54.4 grams (0.4 mol) of sodium acetate trihydrate. The mixture is stirred for 20 minutes at room temperature to insure neutralization of the hydrochloride salt resulting in the formation of a suspension of equimolar amounts of cysteine and sodium acetate.

The mixture is then chilled to 3°-6°C by external cooling and 20 ml (20.8 grams, 0.21 mol) of acetic anhydride is added thereto in dropwise fashion with cooling in the above range. The resulting mobile suspension is stirred for 6 hours at room temperature, allowed to stand overnight, and finally heated at reflux (72°C) for 4 hours. The resulting suspension of sodium N-acetyl-L-cysteinate is then neutralized by treatment at 5°-10°C with 8 grams of hydrogen chloride. Resulting sodium chloride is removed by filtration and the product is isolated by distilling the solvent from the filtrate in vacuo and crystallizing the residue from 35 ml of water, yield 26.3 grams (80.6%) of N-acetylcysteine as a white solid, MP 109°-110°C.

References

Merck Index 82
Kleeman & Engel p. 8
PDR p. 1126
DOT 16 (2) p. 42 (1980)
I.N. p. 8
REM p. 867
Martin, T.A. and Waller, C.W.; U.S. Patent 3,184,505; May 18, 1965; assigned to Mead Johnson & Company.

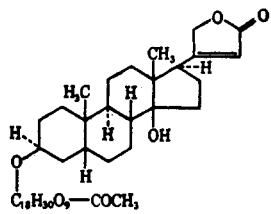
ACETYLDIGITOXIN

Therapeutic Function: Cardiotonic

Chemical Name: See structural formula

Common Name: Digitoxin monoacetate

Structural Formula:



Chemical Abstracts Registry No.: 1111-39-3

Trade Name	Manufacturer	Country	Year Introduced
Acylanid	Sandoz	U.S.	1954
Acygoxine	Sandoz	France	1972
Acylanide	Sandoz	France	1954
Acylanil	—	—	—
Acylanid	Sandoz	Italy	1966
Sandolanid	Sandoz	W. Germany	1968

Raw Materials

Digitalis Ferruginea Leaves

Manufacturing Process

Acetyldigitoxin-α can be obtained from acetyldigitoxin-β by heating it in an anhydrous or aqueous organic solvent at neutral, weakly acid or weakly alkaline pH, i.e., at a pH range from about 3.5 to about 8.

The acetylidigitoxin-β used for this purpose is a cardiac glycoside which can be obtained either by splitting off the glucose residue from lanatoside A, or by extraction of the leaves of *Digitalis ferruginea.* It is composed of the aglycone digitoxigenin and 3 molecules of digitoxose, to one of which an acetyl group is attached. Acetyldigitoxin-α, obtained from acetyldigitoxin-β by rearrangement, differs from the latter in the position of the acetyl group.

The process may be carried out, for example, in the following manner: A solution of acetyldigitoxin-β in a suitable solvent, such as methanol, is boiled under reflux and then diluted with water. The unchanged acetyldigitoxin-β, which crystallizes out first, is filtered off and can again be submitted to the same process. On concentrating the filtrate, acetyldigitoxin-α separates out in crystalline form and after filtering off and recrystallizing is obtained in a pure state. The acetyldigitoxin-α crystallizes from aqueous methanol in platelets melting at 217°-221°C.

References

Merck Index 83
Kleeman & Engel p. 9
I.N. p. 8
Stoll, A. and Kreis, W.; U.S. Patent 2,776,963; January 8, 1957; assigned to Sandoz, AG, Switzerland.

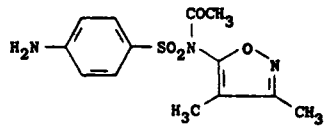
ACETYL SULFISOXAZOLE

Therapeutic Function: Antimicrobial

Chemical Name: N-[(4-aminophenyl)sulfonyl]-N-(3,4-dimethyl-5-isoxazolyl)sulfanilamide

Common Name: Acetylsulfafurazol

Structural Formula:



Chemical Abstracts Registry No.: 80-74-0

Trade Name	Manufacturer	Country	Year Introduced
Gantrisin Acetyl	Roche	U.S.	1954
Lipo-Gantrisin Acetyl	Roche	U.S.	1954
Pediazole	Ross	U.S.	—

Raw Materials

Sulfisoxazole
Acetic Anhydride

Manufacturing Process

267 grams (1 mol) of sulfisoxazole were suspended in 400 ml of acetone and 79 grams (1 mol) of dry pyridine at 20°-25°C in a round-bottom flask equipped with a stirrer and thermometer. 132 grams (1 mol) of acetic anhydride were added within 3 minutes with stirring. The sulfisoxazole dissolved in the mixture and a clear solution resulted. The temperature rose to 39°-40°C. After stirring for several minutes, the product started to crystallize as a white crystalline mush. The temperature rose to 42°-43°C, maintained itself at this temperature for 15-30 minutes, and then started to drop. Stirring was continued for 5 hours and the mixture was then allowed to stand for 10 hours. One liter of 2.5-3.0% ice-cold aqueous ammonia and some fresh ice were then added while stirring and the crystals were filtered without delay. The crystals were washed on the filter with 1 liter of ice-cold 1% ammonia and then with 1 liter of water. The material on the filter was well pressed off, washed with 200-300 ml of alcohol and dried at 70°C to constant weight. The N-monoacetyl sulfisoxazole melted at 193°-194°C and showed a positive Bratton-Marshall reaction and a positive Hucknall-Turfat reaction.

The product is in the form of colorless crystals which are somewhat water repellent. It is insoluble in alkali but is saponified upon standing in alkaline suspension (3% ammonia). It is soluble in strong acids (20-36% HCl or 10 N H_2SO_4) and is rapidly saponified upon standing.

References

Merck Index 104
Kleeman & Engel p. 13
PDR pp. 1487, 1558
I.N. p. 10
Hoffer, Max; U.S. Patent 2,721,200; October 18, 1955; assigned to Hoffmann-La Roche Inc.

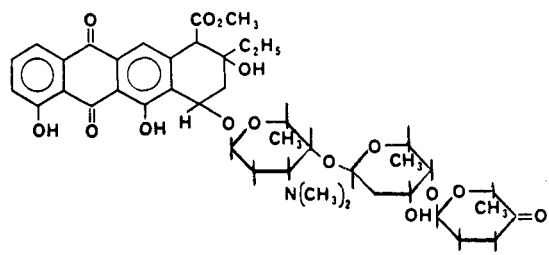
ACLARUBICIN

Therapeutic Function: Antitumor; antibiotic

Chemical Name: [1R-(1α,2β,4β)]-2-Ethyl-1,2,3,4,6,11-hexahydro-2,5,7-trihydroxy-6,11-dioxo-4-[[O-2,3,6-trideoxy-α-L-glycero-hexopyranos-4-ulos-1-yl-(1→4)-O,2,6-dideoxy-α-L-lyxohexopyranosyl-(1→4)-2,3,6-trideoxy-3-(dimethylamino)-α-L-lyxohexopyranosyl]-oxy]-1-naphthacenecarboxylic acid methyl ester

Common Name: Aclacinomycin A

Structural Formula:



Chemcal Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Aclacinon	Yamanouchi	Japan	1981
Aclacinomycine	Roger Bellon	France	1981

Raw Materials

Carbohydrates (By Fermentation)

Manufacturing Process

An aqueous medium having the following composition was prepared:

	Percent
Potato starch	1
Glucose	1
Prorich	1.5
KH_2PO_4	0.1
K_2HPO_4	0.1
$MgSO_4 \cdot 7H_2O$	0.1
NaCl	0.3
Minerals*	0.125
Silicone (KM75)	0.05
pH	7.0

*2.8 g $CuSO_4 \cdot 5H_2O$, 0.4 g $FeSO_4 \cdot 7H_2O$, 3.2 g $MnCl_2 \cdot 4H_2O$, 0.8 g $ZnSO_4 \cdot 7H_2O$ in 500 ml water

100 ml of this medium was sterilized at 120°C for 15 min in a 500 ml Sakaguchi-shaking flask which was inoculated from an agar slant culture of *Streptomyces galilaeus* MA144-M1 by platinum loop. Incubation proceeded for 48 hr at 28°C on a reciprocal shaker. 10 ℓ of the previously sterilized medium in a 20 ℓ stainless steel jar fermenter were aseptically inoculated with 200 ml of the above seed cultures. Fermentation was carried out at 28°C for 32 hours with agitation (240 rpm) and aeration (5 ℓ/min). The cultured broth obtained was adjusted to pH 4.5, mixed with an adsorbent siliceous earth material and filtered from the mycelium. The filtrate and cake obtained thereby were extracted separately. The cake was suspended in acetone (3 ℓ/kg wet cake), stirred for 2 hr and filtered, and the cake was further extracted with acetone once again. The extracts thus obtained were evaporated to one-tenth volume in vacuo. The culture filtrate was adjusted to pH 6.8 and extracted twice with one-third volume of ethyl acetate, and the ethyl acetate extracts were concentrated to one-tenth volume in vacuo.

Twenty grams of the resulting oily substances were mixed with 20 grams of silicic acid (Mallinckrodt Chemical Co.), applied to a column 40 cm in length and 4.5 cm in diameter filled with silicic acid, and eluted with a benzene-acetone-methanol mixture. The initial eluate which eluted with a 1:1:0 mixture was discarded and the active fractions eluted with 1:3:0 and 1:3:0.3 mixtures were collected and concentrated to dryness in vacuo. 11.5 g of this crude substance was then dissolved in a small amount of ethyl acetate and applied to the same silicic acid column as above. After discarding the initial eluates by the 1:1 and 2:1 benzene-acetone mixtures, aclacinomycin B fractions were first eluted with the above mixtures of 1:3 and 1:5 ratio, and aclacinomycin A fractions were then eluted with the 1:5:0.5 and 1:5:1 benzene-acetone-methanol mixtures. The eluates were dried over anhydrous sodium sulfate and concentrated to dryness in vacuo. 4.8 g of crude aclacinomycin A and 3.5 g of aclacinomycin B were obtained as yellow powder.

2.0 g of crude aclacinomycin A obtained as above were dissolved in a small amount of chloroform, applied to a column 20 cm in length and 20 cm in diameter filled with 30 g of silicic acid. After eluting off the pigments containing aglycone and aclacinomycin B and other impurities with chloroform and 1.5% methanol-containing chloroform, aclacinomycn A fractions

were eluted with 2% methanol-containing chloroform, and concentrated to dryness in vacuo. 53 mg of yellow powder of aclacinomycin A was obtained. Its melting point was 129° to 135°C.

References

DFU 2 (3) 171 (1978) (as Aclacinomycin A)
DOT 18 (10) 517 (1982)
I.N. p. 42 (1984)
Umezawa, H., Takeuchi, T., Hamada, M., Takamatsu, A. and Oki, T.; U.S. Patent 3,988,315; October 26, 1976; assigned to Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai

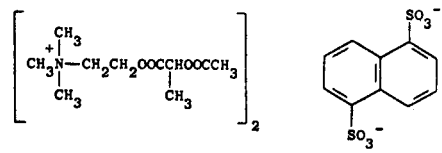
ACLATONIUM NAPADISYLATE

Therapeutic Function: Cholinergic

Chemical Name: 2-[2-(Acetyloxy)-1-oxopropoxy]-N,N,N-trimethylethanaminium-1,5-naphthalenedisulfonate(2:1)

Common Name: Bis[Acetoxy-methyl acetic acid trimethylammoniumethyl ester]-naphthalene-1,5-disulfonate

Structural Formula:



Chemical Abstracts Registry No.: 55077-30-0

Trade Name	Manufacturer	Country	Year Introduced
Abovis	Toyama	Japan	1981

Raw Materials

Bis(Choline)-Naphthalene-1,5-Disulfonate
Lactic Acid Anhydride Diacetate

Manufacturing Process

5.2 g of bis(choline)-naphthalene-1,5-disulfonate was suspended in 30 ml of acetonitrile, and 10 g of lactic acid anhydride diacetate was added thereto. This mixture was refluxed for 3 hours. The resulting reaction mixture was allowed to stand at room temperature while cooling to precipitate the desired product crystals, which were collected by filtration. 5.5 g (76% yield) of the desired product having a melting point of 189° to 191°C were obtained.

References

Merck Index 110
DFU 7 (4) 227 (1982)
DOT 19 (1) 8 (1983)
I.N. p. 42
Miura, K., Takagawa, N., Suzuki, Y. and Matsumoto, Y.; U.S. Patent 3,903,137; September 2, 1975; assigned to Toyama Chemical Co., Ltd.

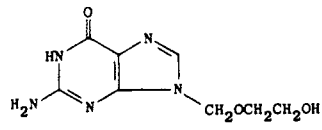
ACYCLOVIR

Therapeutic Function: Antiviral

Chemical Name: 2-Amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one

Common Name: Acycloguanosine; 9-(2-hydroxyethoxymethyl)guanine

Structural Formula:



Chemical Abstracts Registry No.: 59277-89-3

Trade Name	Manufacturer	Country	Year Introduced
Zovirax	Burroughs-Wellcome	U.K.	1981
Zovirax	Burroughs-Wellcome	U.S.	1982
Zovirax	Burroughs-Wellcome	Switz.	1982
Zovirax	Burroughs-Wellcome	W. Germany	1983
Zovirax	Burroughs-Wellcome	Sweden	1983
Zovirax	Burroughs-Wellcome	France	1983

Raw Materials

Sodium Nitrite
2-Chloro-9-(2-Hydroxyethoxymethyl)adenine
Ammonia

Manufacturing Process

Solid sodium nitrite (0.97 g) was added at room temperature with stirring over a period of one hour to a solution of 2-chloro-9-(2-hydroxyethoxymethyl)adenine (0.5 g) in glacial acetic acid (10 ml). The reaction mixture was stirred for an additional 4½ hours. The white solid was removed by filtration, washed with cold acetic acid and then well triturated with cold water to remove the sodium acetate present. The solid product was retained. The combined acetic acid filtrate and wash was evaporated at reduced pressure and 40°C bath temperature and the residual oil triturated with cold water. The resulting solid material was combined with the previously isolated solid and the combined solids dried and recrystallized from ethanol to give 2-chloro-9-(2-hydroxyethoxymethyl)-hypoxanthine (0.25 g), MP>310°C. Elemental analysis and NMR spectrum were consistent with this structure.

A mixture of 2-chloro-9-(2-hydroxyethoxymethyl)-hypoxanthine (0.375 g) and methanol (80 ml) saturated with anhydrous ammonia was heated in a bomb at 125°C for 5 hours. The bomb was cooled in an ice bath and the reaction mixture removed. Solvent and excess ammonia were removed under reduced pressure at 50°C. After the residue was triturated with cold water to remove the ammonium chloride formed, the remaining solid was dried and then recrystallized from methanol to give pure 9-(2-hydroxyethoxymethyl)guanine (0.24 g), MP 256.5°-257°C.

References

Merck Index 140
DFU 4 (11) 842 (1979)
Kleeman & Engel p. 14
PDR p. 773
OCDS Vol. 3 p. 229

DOT 18 (2) 52 (1982)
REM p. 1231
Schaeffer, H.J.; U.S. Patent 4,199,574; April 22, 1980; assigned to Burroughs-Wellcome Co.

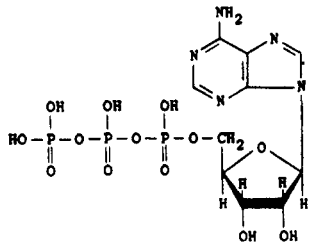
ADENOSINE TRIPHOSPHATE

Therapeutic Function: Coenzyme; vasodilator

Chemical Name: Adenosine 5'-(tetrahydrogen triphosphate)

Common Name: ATP; Triphosadenine

Structural Formula:



Chemical Abstracts Registry No.: 56-65-5

Trade Name	Manufacturer	Country	Year Introduced
Atepodin	Medix	Spain	–
Atriphos	Biochimica	Switz.	–
Estriadin	Boizot	Spain	–
Striadyne	Auclair	France	–
Triphosphodine	I.C.I.	U.K.	–

Raw Materials

1,3-Dicyclohexylguanidinium adenosine 5'-phosphoramidate
Bis-Triethylammonium pyrophosphate

Manufacturing Process

With a solution of 0.29 part by weight of well dried 1,3-dicyclohexylguanidinium adenosine 5'-phosphoramidate in 5 parts by volume of ortho-chlorophenol is admixed a solution of 0.95 part by weight of bis-triethylammonium pyrophosphate in a mixed solvent composed of 1 part by volume of ortho-chlorophenol and 2 parts by volume of acetonitrile. The mixture is left standing at 20°C for 2 days. Then 30 parts by volume of water is added to the mixture. After washing with three 15 parts by weight volume-portions of diethyl ether, the aqueous layer is separated, and the remaining diethyl ether in the aqueous layer is removed under reduced pressure. Five parts by weight of activated charcoal is added to the aqueous layer and the mixture is stirred for 30 minutes. The activated charcoal is filtered and further 1 part by weight of activated charcoal is added to the filtrate. After 20 minutes agitation, the activated charcoal is taken out by filtration. The combined activated charcoal is washed with a little water, and eluted twice with respective 300 and 200 parts by volume-portions of 50% (volume) ethanol containing 2% (volume) of concentrated aqueous ammonia. The eluate is concentrated

to 40 parts by volume, then is passed through a column packed with 20 parts by volume of a strongly basic anion exchange resin in bead form (chloric type) (polystyrene trimethylbenzyl ammonium type resin sold under the name of Dowex-1 from Dow Chemical Company, Mich. U.S.A.). Then, the column is washed with 750 parts by volume of an acid aqueous saline solution containing 0.01 normal hydrochloric acid and 0.02 normal sodium chloride and then eluted with 600 parts by volume of an acid aqueous saline solution composed of 0.01 normal hydrochloric acid and 0.2 normal sodium chloride. After neutralizing with a diluted sodium hydroxide solution, the eluate is treated with activated charcoal to adsorb ATP as its sodium salt. The separated activated charcoal is washed with water and eluted with 60% (volume) ethanol containing 2% (volume) of concentrated aqueous ammonia. The eluate is concentrated to 0.5 part by volume, then 5 parts by volume of ethanol is added. The precipitate thus deposited is centrifuged and dried at low temperature to obtain 0.155 part by weight of tetrasodium salt of ATP containing 4 mols of water of crystallization as a colorless crystalline powder. The yield is 47% relative to the theoretical.

References

Merck Index 146
I.N.p. 983
Tanaka, K. and Honjo, M.; U.S. Patent 3,079,379; February 26, 1963; assigned to Takeda Pharmaceutical Industries, Ltd.

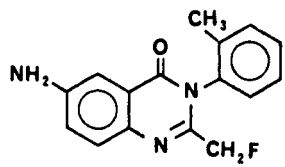
AFLOQUALONE

Therapeutic Function: Centrally acting muscle relaxant

Chemical Name: 6-Amino-2-(fluoromethyl)-3-(o-tolyl)-4(3H)-quinazolinone

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 56287-74-2; 56287-75-3 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Arofuto	Tanabe Seiyaku	Japan	1983

Raw Materials

N-(2-Amino-5-Nitrobenzyl)-o-Toluidine
Fluoroacetyl Chloride
Acetic Anhydride
Hydrogen

Manufacturing Process

14.4 g (0.053 mol) of N-(2-amino-5-nitrobenzoyl)-o-toluidine and 6.3 g (0.08 mol) of pyridine are dissolved in 300 ml of tetrahydrofuran. 12.2 g (0.126 mol) of fluoroacetyl chloride

are added to the solution for 10 minutes under ice-cooling. The solution is stirred at the same temperature for 30 minutes and then at room temperature for 2.5 hours. The reaction solution is allowed to stand at room temperature overnight. The crystalline precipitate is collected by filtration, washed with water and then dried. 16.4 g of N-(2-fluoroacetamido-5-nitrobenzoyl)-o-toluidine are obtained. Yield: 93.7%; MP 238°-239°C.

16.5 g (0.05 mol) of N-(2-fluoroacetamido-5-nitrobenzoyl)-o-toluidine and 25.5 g (0.25 mol) of acetic acid anhydride are dissolved in 250 ml of glacial acetic acid. The solution is refluxed for 2 hours under heating. Then, the reaction solution is evaporated to remove solvent. The residue thus obtained is poured into ice-water, and the aqueous mixture is adjusted to pH 9 with potassium carbonate. The crystalline precipitate is collected by filtration. 15.5 g of 2-fluoromethyl-3-(o-tolyl)-6-nitro-4(3H)-quinazolinone are obtained. Yield: 98.7%; MP 155°-158°C (recrystallized from ethanol).

A mixture of 2.0 g (0.064 mol) of 2-fluoromethyl-3-(o-tolyl)-6-nitro-4(3H)-quinazolinone, 0.2 g of 5% palladium-carbon and 100 ml of acetic acid is shaken for 30 minutes in hydrogen gas. The initial pressure of hydrogen gas is adjusted to 46 lb and the mixture is heated with an infrared lamp during the reaction. After 30 minutes of this reaction, the pressure of hydrogen gas decreases to 6 lb. After the mixture is cooled, the mixture is filtered to remove the catalyst. The filtrate is evaporated to remove acetic acid, and the residue is dissolved in chloroform. The chloroform solution is washed with 5% aqueous sodium hydroxide and water, successively. Then, the solution is dried and evaporated to remove solvent. The oily residue thus obtained is dissolved in 2 ml of chloroform, and the chloroform solution is passed through a column of 200 g of silica gel. The silica gel column is eluted with ethyl acetate-benzene (1:1). Then, the eluate is evaporated to remove solvent. The crude crystal obtained is washed with isopropylether and recrystallized from isopropanol. 0.95 g of 2-fluoromethyl-3-(o-tolyl)-6-amino-4(3H)-quinazolinone is obtained. Yield: 52.5%; MP 195°-196°C.

References

DFU 7 (8) 539 (1982)
DOT 19 (1) 581 (1983)
Inoue, L., Oine, T., Yamado, Y., Tani, J., Ishida, R. and Ochiai, T.; U.S. Patent 3,966,731; June 29, 1976; assigned to Tanabe Seiyaku Co., Ltd.

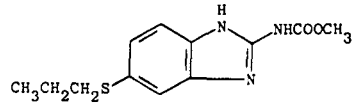
ALBENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: [5-(Propylthio)-1H-benzimidazol-2-yl] carbamic acid methyl ester

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 54965-21-8

Trade Name	Manufacturer	Country	Year Introduced
Zentel	SK&F	France	1981

Raw Materials

3-Chloro-6-Nitroacetanilide
Propyl Mercaptan
Hydrogen
Cyanamide
Methyl Chloroformate

Manufacturing Process

A mixture of 6.65 g of 3-chloro-6-nitroacetanilide, 3.2 ml of propylmercaptan, 5.6 g of 50% sodium hydroxide and 100 ml of water is heated at reflux overnight. The cooled mixture is filtered to give the desired 2-nitro-5-propylthioaniline, MP 69.5°-71.5°C after recrystallization from ethanol then hexane-ether. NMR ($CDCl_3$) 40%.

The aniline (2.5 g) is hydrogenated with 1.9 ml of concentrated hydrochloric acid, 100 ml ethanol and 5% palladium-on-charcoal to give 4-propylthio-o-phenylene-diamine hydrochloride.

A mixture of 2.5 ml of 50% sodium hydroxide in 5 ml of water is added to a mixture of 1.9 g of cyanamide, 2.2 g of methylchloroformate, 3.5 ml of water and 3 ml of acetone over 45 minutes below 10°C, pH raised to 6.5. A molar equivalent solution of the diamine in 100 ml of ethanol is added. The mixture is heated until the easily volatile solvents are expelled, to about 85°C, then maintained at this temperature with some water added for one-half hour. The product, methyl 5-propylthio-2-benzimidazolecarbamate, is separated, washed to give a colorless crystalline solid, MP 208°-210°C.

References

Merck Index 197
DFU 2 (2) 81 (1977)
OCDS Vol. 2 p. 353 (1980)
DOT 15 (3) 89 (1979)
I.N. p. 50
Gyurik, R.J. and Theodorides, V.J.; U.S. Patent 3,915,986; October 28, 1975; assigned to Smith Kline Corp.

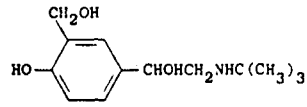
ALBUTEROL

Therapeutic Function: Bronchodilator

Chemical Name: α^1-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol

Common Name: Salbutamol; α'-tert-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol

Structural Formula:



Chemical Abstracts Registry No.: 18559-94-9; 51022-70-9 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Ventolin	Allen & Hanburys	U.K.	1969
Sultanol	Glaxo	W. Germany	1971
Ventoline	Glaxo	France	1971
Ventolin	Glaxo	Italy	1973
Ventolin	Sankyo	Japan	1973
Ventolin	Glaxo	Switz.	1981
Ventolin	Glaxo	U.S.	1981

Trade Name	Manufacturer	Country	Year Introduced
Broncollenas	Llenas	Spain	–
Buto-Asma	Aldo Union	Spain	–
Proventil	Schering	U.S.	–
Rotacaps	Schering	–	–
Salbumol	Medica	Finland	–
Salbutol	Iltas	Turkey	–
Salbuvent	Leiras	Finland	–
Salbuvent	Nyegaard	Norway	–

Raw Materials

5-(N-benzyl-N-tert-butylglycyl)salicylic acid methyl ester hydrochloride
Lithium aluminum hydride
Hydrogen

Manufacturing Process

(a) α^1-benzyl-tert-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol–3.0 g of 5-(N-benzyl-N-tert-butylglycyl)-salicylic acid methyl ester hydrochloride in 40 ml of water was basified with sodium bicarbonate solution and extracted into ether. The ethereal solution was dried over $MgSO_4$ and evaporated and the basic residue in 20 ml of dry tetrahydrofuran was added with stirring to 1.0 g of lithium aluminium hydride in 100 ml of dry tetrahydrofuran, over a period of 5 minutes. The light gelatinous precipitate that formed was stirred and refluxed for 8 hours after which time 7 ml of water was carefully added and the solvents were removed under reduced pressure.

The residue was acidified with dilute hydrochloric acid and brought to pH 8 with sodium hydroxide and sodium bicarbonate. The mixture was filtered and the filtrate and orange solid were separately extracted with chloroform. The combined, dried, chloroform solutions were evaporated to give 2.2 g of the crude basic triol as an orange solid, when triturated with ether. A portion of the material was recrystallized from ether/light petroleum (BP 40°–60°C) to give a white solid, MP 109°–111°C.

In an alternative process, sodium borohydride was used as the reducing agent, as follows:

36 g of 2-(benzyl-tert-butylamino)-4'-hydroxy-3'-hydroxymethyl acetophenone, hydrochloride was shaken with 100 ml of 10% sodium carbonate solution and 100 ml of ethyl acetate. The ethyl acetate layer was separated, washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo.

The residual gum was dissolved in 360 ml of ethanol and cooled to 15°C in an ice/water bath, 8 g of sodium borohydride was then added in portions over 30 minutes while maintaining the temperature at 15°–20°C. After a further 30 minutes at 20°C the solution was stirred at room temperature for 2 hours. The solution was again cooled in ice and 250 ml of 2 N sulfuric acid were slowly added, then the solution was evaporated in vacuo until the ethanol had been removed. The clear aqueous solution was then treated with 250 ml of 10% sodium carbonate solution and the oil which precipitated was extracted into ethyl acetate. The ethyl acetate layer was washed with sodium carbonate solution, then with water, and was dried over anhydrous sodium sulfate and evaporated in vacuo, to a small volume. Petroleum ether (BP 40°–60°C) was added, and after standing overnight a white solid was obtained. This was filtered off to give 23 g of the product, MP 110°–114°C.

(b) α^1-tert-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol–0.8 g of α^1-benzyl-tert-butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol in 20 ml of ethanol and 2 ml of water was shaken with hydrogen in presence of 0.50 g of pre-reduced 10% palladium on charcoal catalyst. When uptake of hydrogen was complete, the solution was filtered and evaporated under reduced pressure to give 0.4 g of the base as a colorless oil which yielded a white solid, MP 144°–145°C when triturated with ether/cyclohexane. Recrystallization from ethyl acetate-cyclohexane gave a white solid, MP 147°–149°C.

References

Merck Index 206
DFU 4 (9) 629 (1979)
Kleeman & Engel p. 813
PDR 40 pp. 916, 1649
OCDS Vol. 2 p. 43 (1980)
DOT 16 (8) 269 (1980)
I.N. p. 860
REM p. 881
Lunts, L.H.C. and Toon, P.; U.S. Patent 3,644,353; February 22, 1972; assigned to Allen & Hanburys Ltd.

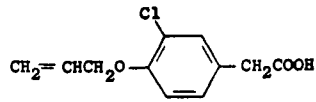
ALCOFENAC

Therapeutic Function: Antiinflammatory

Chemical Name: 3-Chloro-4-(2-propenyloxy)benzene-acetic acid

Common Name: [4-(allyloxy)-3-chlorophenyl] acetic acid

Structural Formula:



Chemical Abstracts Registry No.: 22131-79-9

Trade Name	Manufacturer	Country	Year Introduced
Mervan	Cooper	Switz.	–
Prinalgin	Berk	U.K.	1971
Neoston	Beiersdorf	W. Germany	1972
Allopydin	Chugai	Japan	1976
Zumaril	Abbott	Italy	1976
Epinal	Kyorin	Japan	1976
Darkeyfenac	Cuatrecasas-Darkey	Spain	–
Desinflam	Sintyal	Argentina	–
Medifenac	Medici	Italy	–
Mervan, Mirvan	Continental Pharma	Belgium	–
Vanadian	Federico Bonet	Spain	–
Zumaril	Sidus	Italy	–
Rentenac	Tosi	Italy	–

Raw Materials

3-Chloro-4-allyloxyphenyl acetonitrile
Potassium hydroxide

Manufacturing Process

103.7 grams of 3-chloro-4-allyloxyphenylacetonitrile in 500 cc of ethanol, 100 grams of potassium hydroxide and 100 cc of water are refluxed for 4 hours. Maximum of alcohol is evaporated, the residue is diluted with water and ice, and acidified with 20% HCl. The solid is filtered and washed with petroleum ether. 91.5 grams of acid are obtained (Yield: 81%) which is recrystallized from aqueous methanol; MP 92°-93°C.

References

Merck Index 209
Kleeman & Engel p. 19
OCDS Vol. 2 p. 68 (1980)
DOT 8 No. 9, 329 (1972)
I.N. p. 50
British Patent 1,174,535; December 17, 1969; assigned to Madan AG, Switzerland.

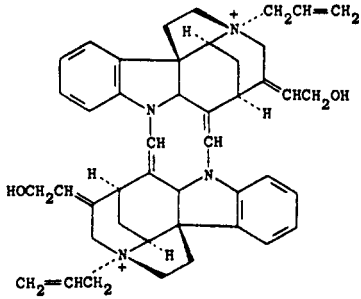
ALCURONIUM CHLORIDE

Therapeutic Function: Skeletal Muscle Relaxant

Chemical Name: N,N'-Diallylnortoxiferinium Dichloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 15180-03-7

Trade Name	Manufacturer	Country	Year Introduced
Alloferin	Roche	U.K.	1966
Alloferin	Roche	W. Germany	1968
Alloferine	Roche	France	1968
Dialferin	Nippon Roche	Japan	1969
Toxiferin	Roche	–	–

Raw Materials

Diallyl Nortoxiferine Diiodide
Chloride Ion Exchange Resin

Manufacturing Process

31 g of diallylnortoxiferine diiodide are suspended in 1 liter of water and shaken with 1,100 ml of Amberlite IRA-400 [chloride ion form, described Merck Index, 7th edition, Merck & Co., Inc., Rahway, New Jersey (1960), page 1584], for 2 hours. The diiodide thereby goes into solution. The ion exchanger is filtered off and then washed in 3 portions with a total of 1 liter of water. The combined filtrates are then allowed to run through a column of 300 ml of Amberlite IRA-400 (chloride ion form), rinsed with 300 ml of water and the eluate evaporated to dryness in a vacuum while excluding air. The residue gives on recrystallization from methanol/ethanol crystalline pure colorless diallylnortoxiferine dichloride in a yield of 18.6 g. The compound contains 5 mols of water of crystallization after equilibration in air.

References

Merck Index 215
Kleeman & Engel p. 19
I.N. p. 51
Boller, A., Els, H. and Furst, A.; U.S. Patent 3,080,373; March 5, 1963; assigned to Hoffman La Roche, Inc.

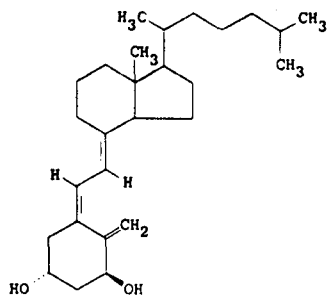
ALFACALCIDOL

Therapeutic Function: Calcium Regulator, Vitamin D

Chemical Name: 9,10-Secocholesta-5,7,10(19)-triene-1,3-diol

Common Name: 1α-Hydroxycholecalciferol; 1α-Hydroxyvitamin D_3

Structural Formula:



Chemical Abstracts Registry No.: 41294-56-8

Trade Name	Manufacturer	Country	Year Introduced
One-Alpha	Leo	U.K.	1978
Eins-Alpha	Thomae	W. Germany	1980
Alfarol	Chugai	Japan	1981
One-Alpha	Teljin	Japan	1981
Delakmin	Roussel	France	—
Etalpha	Leo	Denmark	—
Un-Alfa	Leo	—	—

Raw Materials

Cholesta-1,5,7-trien-3β-ol
4-Phenyl-1,2,4-triazoline-3,5-dione
m-Chloroperbenzoic Acid
Lithium Aluminum Hydride

Manufacturing Process

1. Preparation of 1,4-cyclized adduct of cholesta-1,5,7-trien-β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione: a solution of 400 mg of cholesta-1,5-7-trien-3β-ol in 30 ml of tetrahydrofuran is cooled with ice, and 190 mg of 4-phenyl-1,2,4-triazoline-3,5-dione is added little by little to the solution under agitation. The mixture is agitated at room temperature for 1 hour and the solvent is distilled under reduced pressure. The residue is purified by chromatography using a column packed with silica gel. Fractions eluted with ether-hexane (7:3 v/v) are collected and recrystallization from ether gives 550 mg of a 1,4-cyclized adduct of cholesta-1,5,7-trien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione having a melting point of 178° to 182°C.

2. Preparation of 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione: 1.25 g of the 1,4-cyclized adduct of cholesta-1,5,7-trien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione is dissolved in 50 ml of chloroform, and 560 mg of m-chloroperbenzoic acid is added to the solution. The mixture is agitated for 20 hours at room temperature, and 200 mg of m-chloroperbenzoic acid is further added and the mixture is agitated again for 20 hours. The reaction mixture liquid is diluted with chloroform, washed with a 10% aqueous solution of potassium carbonate and dried with magnesium sulfate. Then, the solvent is distilled under reduced pressure. The residue is purified by silica gel chromatography, and first effluent fractions eluted with ether are collected, and recrystallization from methanol gives 680 g of a crystal melting at 172° to 173°C. The second ether effluent fractions are collected, and recrystallization from methanol gives 400 mg of a 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α,2α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione having a melting point of 152° to 154°C.

3. Preparation of cholesta-5,7-diene-1α,3β-diol: a solution of 500 mg of the 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α,2α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione in 40 ml of tetrahydrofuran is added dropwise under agitation to a solution of 600 mg of lithium aluminum hydride in 30 ml of THF. Then, the reaction mixture liquid is gently refluxed and boiled for 1 hour and cooled, and a saturated aqueous solution of sodium sulfate is added to the reaction mixture to decompose excessive lithium aluminum hydride. The organic solvent layer is separated and dried, and the solvent is distilled. The residue is purified by chromatography using a column packed with silica gel. Fractions eluted with ether-hexane (7:3 v/v) are collected, and recrystallization from the methanol gives 400 mg of cholesta-5,7-diene-1α,3β-diol.

4. Preparation of 1α,3β-dihydroxyprovitamin D_3: a solution of 25 mg of cholesta-5,7-diene-1α,3β-diol in 650 ml of ether is subjected to radiation of ultraviolet rays for 14 minutes in an argon gas atmosphere by passing it through a Vycor filter using a 200-W high pressure mercury lamp (Model 654A-36 manufactured by Hanobia). The solvent is distilled at room temperature under reduced pressure. This operation is repeated twice, and 50 mg of the so obtained crude product is fractionated by chromatography using a column packed with 20 g of Sephadex LH-20. The first effluent fractions eluted with chloroform-hexane (65:35 v/v) give 13.5 mg of oily 1α,3β-dihydroxyprovitamin D_3. The composition exhibits a maximum ultraviolet absorption at 260 m in an ether solution.

5. Preparation of 1α-hydroxycholecalciferol: a solution of 13.5 mg of 1α,3β-dihydroxyprovitamin D_3 in 200 ml of ether is allowed to stand still in the dark at room temperature in an argon gas atmosphere for 2 weeks. During this period, the position of the maximum ultraviolet absorption is shifted from 260 mμ to 264 mμ, and the absorption intensity becomes 1.6 times as high as the original intensity. The solvent is distilled at room temperature under reduced pressure, and the residue is purified by chromatography using a column packed with 10 g of Sephadex LH-20. The fractions eluted with chloroform-hexane (65:35 v/v) give 6.5 mg of oily 1α-hydroxycholecalciferol.

References

Merck Index 4730
Kleeman & Engel p. 21
DOT 6 (3) 104 (1970); 14 (10) 441 (1978)
I.N. p. 52
Ishikawa, M., Kaneko, C., Suda, T., Yamada, S., Eguchi, Y., Sugimoto, A. and Sasaki, S.; U.S. Patent 3,929,770; December 30, 1975; assigned to Wisconsin Alumni Research Foundation.

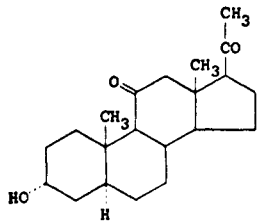
ALFAXALONE

Therapeutic Function: Anesthetic component

Chemical Name: 3-Hydroxypregnane-11,20-dione

Common Name: Alphaxolone

Structural Formula:



Chemical Abstracts Registry No.: 23930-19-0

Trade Name	Manufacturer	Country	Year Introduced
Althesin	Glaxo	U.K.	1972
Alfadion	Nippon Glaxo	Japan	1978
Alfathesin	Glaxo	France	–
Aurantex	Glaxo	W. Germany	–

Raw Materials

3α-Hydroxy-5α-pregn-16-ene-11,20-dione
Hydrogen

Manufacturing Process

A solution of 3α-hydroxy-5α-pregn-16-ene-11,20-dione (200 mg) in freshly distilled tetrahydrofuran (8 ml) with 5% palladium on carbon (100 ml) was hydrogenated until hydrogen uptake ceased. The mixture was filtered through a pad of kieselguhr and the tetrahydrofuran removed in vacuo to give 196 mg, MP 171° to 172°C.

References

Merck Index 225
Kleeman & Engel p. 23
DOT 8 (11) 407 (1972)
I.N. p. 53
Davis, B., Pearce, D.R. and Phillips, G.H., British Patent 1,317,184; May 16, 1973; assigned to Glaxo Laboratories, Ltd.
Davis, B. and Phillips, G.H.; U.S. Patent 3,714,352; January 30, 1973; assigned to Glaxo Laboratories, Ltd.

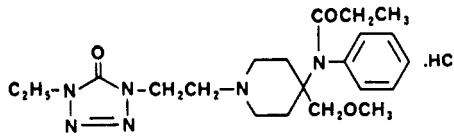
ALFENTANIL HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: N-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropaneamide hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Rapifen	Janssen	Belgium	1983
Rapifen	Janssen	Netherlands	1983
Rapifen	Janssen	W. Germany	1983
Rapifen	Janssen	U.K.	1983
Rapifen	Janssen	Switz.	1983

Raw Materials

1-Ethyl-1,4-dihydro-5H-tetrazol-5-one
1-Bromo-2-chloroethane
N-[4-Methoxymethyl)-4-piperidinyl-N-phenylpropamide

Manufacturing Process

A mixture of 22 parts of 1-ethyl-1,4-dihydro-5H-tetrazol-5-one, 45 parts of 1-bromo-2-chloroethane, 26 parts of sodium carbonate, 0.3 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, water is added and the layers are separated. The aqueous phase is extracted three times with dichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated, yielding 28.4 parts (80%) of 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5H-tetrazol-5-one as a residue.

A mixture of 1.8 parts of 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5H-tetrazol-5-one, 3.45 parts of N-[4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide, 5 parts of sodium carbonate, 0.2 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from 2-propanone, yielding 1.5 parts (33.3%) of N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride monohydrate; melting point 140.8°C.

References

DFU 6 (6) 335 (1981)
OCDS Vol. 3 p. 118 (1984)
DOT 19 (12) 683 (1983)
I.N. p. 53
Janssens, F.; U.S. Patent 4,167,574; September 11, 1979; assigned to Janssen Pharmaceutica NV.

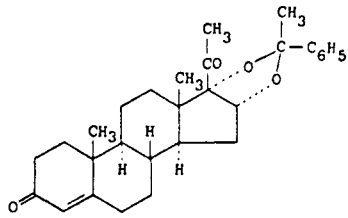
ALGESTONE ACETOPHENIDE

Therapeutic Function: Progestin; Contraceptive

Chemical Name: 16,17-[(1-Phenylethylidene)bis(oxy)] pregn-4-ene-3,20-dione

Common Name: 16α,17α-Dihydroxyprogesterone acetophenide; alphasone acetophenide

Structural Formula:



Chemical Abstracts Registry No.: 24356-94-3

Trade Name	Manufacturer	Country	Year Introduced
Neolutin Depo	Medici	Italy	1982
Neolutin Depositum	Orma	Italy	—
Droxone	Squibb	U.S.A.	—
Decadroxone	Squibb	—	—
Decadroxate	Squibb	—	—

Raw Materials

16α,17α-Dihydroxyprogesterone
Acetophenone

Manufacturing Process

To a suspension of 500 mg of 16α,17α-dihydroxyprogesterone in 25 ml of freshly redistilled acetophenone is added 0.125 ml of 72% perchloric acid and the mixture is agitated at room temperature for one hour. The clear solution is washed with dilute sodium bicarbonate to remove excess acid and the acetophenone layer, after addition of chloroform is separated from the aqueous phase. The organic layer is dried over sodium sulfate and after removal of the chloroform and acetophenone in high vacuum the residue is crystallized from 95% alcohol. The pure acetophenone derivative has a melting point of about 142° to 144°C.

References

Merck Index 227
Kleeman & Engel p. 24
OCDS Vol. 2 p. 171 (1980)
DOT 19 (2) 110 (1983)
I.N. p. 54
Fried, J.; U.S. Patent 2,941,997; June 21, 1960; assigned to Olin Mathieson Chemical Corp.
Fried, J. and Diassi, P.A.; U.S. Patent 3,008,958; November 14, 1961; assigned to Olin Mathieson Chemical Corp.

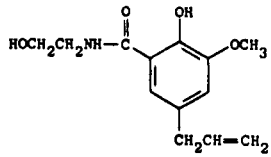
ALIBENDOL

Therapeutic Function: Choleretic; Antispasmodic

Chemical Name: 2-Hydroxy-N-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl)benzamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 26750-81-2

Trade Name	Manufacturer	Country	Year Introduced
Cebera	Bouchara	France	1981

Raw Materials

2-Hydroxy-3-methoxy-5-allyl benzoic acid
Ethanol
Ethanolamine

Manufacturing Process

36 g of ethyl ester of 2-hydroxy-3-methoxy-5-allyl-benzoic acid [obtained by the process described by Pearl, et al., *J. Amer. Chem. Soc.*, Vol 71, 1067-1068 (1949)] and 61 g of ethanolamine were admixed and left to stand for 1 hour at ambient temperature after which it was heated for 1 hour at 120°C. The mixture was extracted with chloroform and the organic phases were washed with half diluted hydrochloric acid, then with water, and the chloroform evaporated off. The residue, after recrystallization from benzene, was a 78% yield of 2-hydroxy-3-methoxy-5-allyl-N-(β-hydroxyethyl)-benzamide having a melting point of 95°C. The product appeared in the form of colorless crystals which were insoluble in water and soluble in dilute sodium hydroxide.

References

Merck Index 230
DOT 18 (10) 525 (1982)
Clemence, F. and Le Martret, O.; U.S. Patent 3,668,238; June 6, 1972; assigned to Roussel Uclaf.

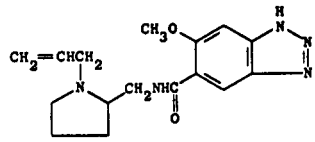
ALIZAPRIDE

Therapeutic Function: Neuroleptic (antiemetic)

Chemical Name: 6-Methoxy-N-[[1-(2-propenyl)-2-pyrrolidinyl] methyl] -H-benzotriazole-5-carboxamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 59338-93-1

Trade Name	Manufacturer	Country	Year Introduced
Plitican	Delagrange	France	1981
Vergentan	Delagrange	W. Germany	1981

Raw Materials

2-Methoxy-4,5-azimido Benzoic Acid
1-Allyl-2-amino-methyl Pyrrolidine
Phosphoric Anhydride

Manufacturing Process

38.6 g (0.2 mol) of 2-methoxy-4,5-azimido benzoic acid were dissolved in anhydrous toluene and 56 g (0.4 mol) of 1-allyl-2-amino-methyl pyrrolidine were added. The mixture was heated to 50°C and then 42 g (0.3 mol) of phosphoric anhydride were added. The mixture was warmed at reflux temperature for 3 hours and then cooled to 80°C. After adding water, the aqueous layer was alkalized. The crystals were filtered, washed with water and then dissolved in 450 ml of acetone. After crystallization, the product was filtered, washed and dried.

40.4 g (yield 65%) of N-(1'-allyl-2'-pyrrolidylmethyl)-2-methoxy-4,5-azimidobenzamide having a melting point of 139°C were obtained.

References

Merck Index 231
DFU 6 (1) 11 (1981)
DOT 18 (4) 162 (1982)
I.N. p. 55
Bulteau, G., Acher, J., Collignon, C. and Monier, J.C.; U.S. Patent 4,039,672; August 2, 1977; assigned to Societe D'Etudes Scientifiques et Industrielles de l'Ile-de-France

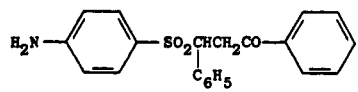
ALKOFANONE

Therapeutic Function: Antidiarrheal

Chemical Name: 3-[(4-Aminophenyl)sulfonyl]-1,3-diphenyl-1-propanone

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 7527-94-8

Trade Name	Manufacturer	Country	Year Introduced
Ciafanone	Roche	U.S.	1956
Alfone	–	–	–

Raw Materials

Benzal Acetophenone
p-Aminobenzene Sulfinic Acid

Manufacturing Process

38 g benzal-acetophenone and 25 g p-aminobenzene-sulfinic acid are refluxed for 5 hours in 700 cc of 85% ethyl alcohol. Fine crystals soon begin to appear and fill the reaction vessel. While still hot, the mixture is suction-filtered. The reaction product is washed first with 750 cc warm absolute alcohol, then with 500 cc water, and finally again with 300 cc alcohol, and then dried in vacuo. Yield 32 g. MP 210°-212°C with decomposition.

References

Merck Index 240
Goldberg, M.W.; U.S. Patent 2,421,836; June 10, 1947; assigned to Hoffmann-La Roche, Inc.

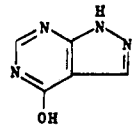
ALLOPURINOL

Therapeutic Function: Xanthine oxidase inhibitor; gout therapy

Chemical Name: 1H-pyrazolo[3,4-d] pyrimidin-4-ol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 315-30-0

Trade Name	Manufacturer	Country	Year Introduced
Zyloprim	Burroughs Wellcome	U.S.	1966
Zyloric	Wellcome	Switz.	—
Zyloric	Burroughs-Wellcome	U.K.	1966
Zyloric	Wellcome	W. Germany	1967
Zyloric	Wellcome	Italy	1968
Zyloric	Wellcome	Japan	1969
Zyloric	Wellcome	France	1969
Lopurin	Boots	U.K.	1980
Adenock	Tanabe	Japan	—
Adenock	Shiraimatsu	Japan	—
Allopin	Yeni	Turkey	—
Allomaron	Nattermann	W. Germany	—
Alloprim	Iltas	Turkey	—
Alloprin	ZCN	Canada	—
Allopur	Gea	Denmark	—
Allopur	Nyegaard	Norway	—
Allopurinol	Sigfried	W. Germany	—
Allopurinol	Efeka	W. Germany	—
Allopurinol	Woelm Pharma	W. Germany	—
Allopurinol	Lederle	Japan	—
Allopurinol	Kowa	Japan	—
Allopurinol	Showa	Japan	—
Allorin	Towa	Japan	—
Allozym	Sawai	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Allural	Nativelle	Italy	–
Allural	Pan Quimica	Spain	–
Allurit	Schoum	Italy	–
Aloc	Toho Iyaku	Japan	–
Alositol	Tanabe	Japan	–
Anoprocin	Nippon Shoji	Japan	–
Antigot	Yurtoglu	Turkey	–
Anzief	Nippon Chemiphar	Japan	–
Aprinol	Daisan	Japan	–
Apurin	Gea	Denmark	–
Apurin	Medica	Finland	–
Apurol	Siegfried	Switz.	–
Bleminol	Desitin	W. Germany	–
Caplenal	Berk	U.K.	–
Capurate	Fawns & McAllan	Australia	–
Cellidrin	Hennig	W. Germany	–
Cosuric	DDSA	U.K.	–
Dabroson	Hoyer	W. Germany	–
Embarin	Diabetylin	W. Germany	–
Epidropal	Fresenius	W. Germany	–
Flogorex	Lancet	Italy	–
Foligan	Henning	W. Germany	–
Geapur	Gea	Denmark	–
Gichtex	Gerot	Austria	–
Ketawrift	Ohta	Japan	–
Ketobun A	Isei	Japan	–
Lopurin	Generics Corp.	U.S.	–
Lysuron	Boehringer Mannheim	W. Germany	–
Masaton	Zensei	Japan	–
Melianin	Kohjin	Japan	–
Mephanol	Mepha	Switz.	–
Milurit	Egyt	Hungary	–
Monarch	SS Pharmaceutical	Japan	–
Nektronan	ICN Pharma	W. Germany	–
Neufan	Teikoku	Japan	–
Neufan	Teisan	Japan	–
Novopurol	Novopharm	Canada	–
Progout	Protea	Australia	–
Puricos	Lennon	S. Africa	–
Purinol	Horner	Canada	–
Riball	Mitsui	Japan	–
Roucol	Rougier	Canada	–
Serviprinol	Servipharm	Switz.	–
Suspendol	Merckle	W. Germany	–
Takanarumin	Takata	Japan	–
Urbol	Heilit	W. Germany	–
Urbol	Gea	Denmark	–
Uredimin	Chassot	Switz.	–
Uricemil	Farnex	Italy	–
Uricemil	Fardeco	Italy	–
Uriconorm	Streuli	Switz.	–
Uridocid	Reig Jofre	Spain	–
Uriscel	Armour Med.	Italy	–
Urobenyl	Endopharm	W. Germany	–
Urolit	Magis	Italy	–
Urosin	Boehringer Mannheim	W. Germany	–
Urozyl-SR	Restan	S. Africa	–
Urtias	Sabona	W. Germany	–

Trade Name	Manufacturer	Country	Year Introduced
Vedatan	Corvi	Italy	–
Xanturat	Grunenthal	W. Germany	–
Zylol	Teva	Israel	–

Raw Materials

Cyanoacetamide
Triethylorthoformate
Morpholine
Hydrazine Hydrate

Manufacturing Process

3-Morpholino-2-cyanoacrylamide: A stirred mixture of cyanoacetamide (63 g), triethylorthoformate (134 g), morpholine (82.5 g) and acetonitrile (37.5 ml) was heated under reflux for 4 hours. The initial reflux temperature was 117°C and the final reflux temperature was 82°C.

At the end of the reflux period the mixture was cooled to 30°C and the heavy crystalline precipitate was collected and washed with 2 X 75 ml of ethanol. The product was dried in vacuo at 30°C. Wt = 111 g. Yield = 82%, MP 173°-175°C.

3-Aminopyrazole-4-carboxamide hemisulfate: To water (253 ml) at 60°C was added 3-morpholino-2-cyanoacrylamide (63.4 g) and 85% technical hydrazine hydrate (22.7 g). The mixture was rapidly heated to 95°C and the temperature was maintained at >90°C for 20 minutes. The mixture was then cooled to 60°C and the pH carefully adjusted to 1.5 by the addition of a mixture of sulfuric acid (45.7 g) and ice (45.7 g). The acidified reaction was cooled to 5°C and the crystalline product collected and washed with cold water (2 X 100 ml) and acetone (2 X 50 ml). The product was dried in vacuo at 80°C. Wt = 5.8 g. Yield = 95%, MP 237°-239°C.

4-Hydroxypyrazolo[3,4-d]pyrimidine: A suspension of 3-aminopyrazole-4-carboxamide hemisulfate (113 g) in formamide (325 g) was stirred and heated to 145°C. The reaction was held at 145°C for 5 hours. The reaction was then cooled to 30°C and the product collected and washed with formamide (2 X 50 ml), water (2 X 150 ml) and acetone (2 X 100 ml). Wt of crude product = 79 g. The crude product was recrystallized by dissolution in a solution made from sodium hydroxide (25 g) in water (1,200 ml) with treatment at 25°C with charcoal (8 g), followed by reprecipitation by the addition of concentrated hydrochloric acid to pH 5. The product was collected and washed with cold water (2 X 300 ml), acetone (2 X 200 ml) and dried in vacuo at 60°C. Wt = 70 g. Yield = 80%.

References

Merck Index 273
Kleeman & Engel p. 27
PDR pp. 685, 774, 830, 993, 1606
OCDS Vol. 1 pp. 152, 269 (1977)
I.N. p. 57
REM p. 1111
Druey, J. and Schmidt, P.; U.S. Patent 2,868,803; January 13, 1959; assigned to Ciba Pharmaceutical Products Inc.
Hitchings, G.H. and Falco, E.A.; U.S. Patent 3,474,098; October 21, 1969; assigned to Burroughs Wellcome & Co.
Cresswell, R.M. and Mentha, J.W.; U.S. Patent 4,146,713; March 27, 1979; assigned to Burroughs Wellcome & Co.

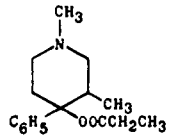
ALPHAPRODINE HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: cis-1,3-dimethyl-4-phenyl-4-piperidinol propanoate hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 77-20-3 (Base); 49638-24-6 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Nisentil	Roche	U.S.	1949

Raw Materials

Lithium
Bromobenzene
1,3-Dimethyl-4-piperidone
Propionic Anhydride
Hydrogen Chloride

Manufacturing Process

In a round-bottom flask provided with stirrer, dropping funnel, condenser and a gas outlet for keeping the system under nitrogen, 200 cc of dry ether is placed and 4.6 grams of lithium cut into thin strips is added. 52 grams of bromobenzene in 50 cc of dry ether are added dropwise and after addition, the mixture is refluxed for 2 hours. This procedure results in the formation of phenyl-lithium. Other aryl-lithium compounds can be prepared in a similar manner by reacting lithium metal or a lithium compound capable of transferring lithium and a compound having an exchangeable halogen group as, for example, bromonaphthalene.

The solution of phenyl-lithium is cooled to -20°C and to this a solution of 12.7 grams of 1,3-dimethyl-4-piperidone, prepared according to the method of Howton, *J. Org. Chem.* 10, 277 (1945), in ether is added dropwise with stirring. After the addition, the stirring is continued for a further 2 hours at -20°C. The lithium complex, 1,3-dimethyl-4-phenyl-4-oxylithium piperidine, which forms is soluble in the ether and can be recovered therefrom. To prepare the piperidinol, the lithium complex, while in the reaction mixture is decomposed by the addition of an ice and hydrochloric acid mixture. The acidified layer is separated, basified and extracted with ether. After drying the ether solution and removing the solvent, the residue on distillation in vacuum distills chiefly at 155°C/10 mm, yielding the product, 1,3-dimethyl-4-phenyl-4-hydroxy piperidine, which, on crystallization from n-hexane melts at 102°C. On treatment with propionic anhydride catalyzed with a trace of sulfuric acid, 1,3-dimethyl-4-propionoxy-4-phenyl piperidine is attained. The latter compound can be converted into the hydrochloride salt by reaction with hydrogen chloride. This salt after crystallization from acetone has a melting point of 209°C.

References

Merck Index 302
Kleeman & Engel p. 29
PDR p. 1494
OCDS Vol. 1 pp. 304 & 2328 (1977)
I.N. p. 60
REM p. 1107
Lee, J. and Ziering, A.; U.S. Patent 2,498,433; February 21, 1950; assigned to Hoffmann-La Roche Inc.