K

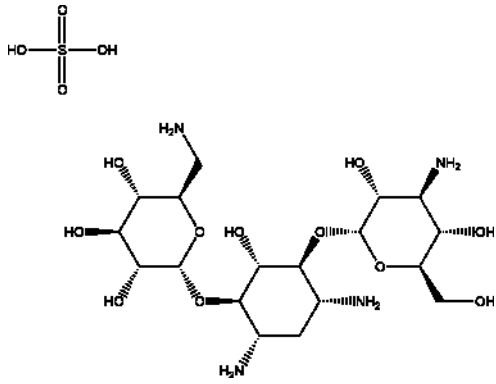
KANAMYCIN SULFATE

Therapeutic Function: Antibacterial

Chemical Name: O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1-6)-O-[6-amino-6-deoxy-α-D-glucopyranosyl-(1-4)-2-deoxy-D-streptamine sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 25389-94-0; 8063-07-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Kantrex	Bristol	US	1958
Kanamycine	Bristol	France	1959
Kanabristol	Bristol	W. Germany	1969
Klebcil	Beecham	US	1979
Enterokanacin	Labif	Italy	-
Kamycine	Bristol	France	-
Kanabiol	Osfa	Italy	-
Kanabiot	Galepharma Iberica	Spain	-
Kanacet	Boniscontro-Gazzone	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Kanacillin	Banyu	Japan	-
Kanacyclin	Banyu	Japan	-
Kanacyn	Continental Pharma	Belgium	-
Kanafil	Farmila	Italy	-
Kanafuracin	Fujita	Japan	-
Kanahidro	Medical	Spain	-
Kanamicina Normon	Normon	Spain	-
Kanamycin	Ferosan	Denmark	-
Kanamytrex	Basotherm	W. Germany	-
Kanapiam	Piam	Italy	-
Kanaqua	Andromaco	Spain	-
Kanasig	Sigma	Australia	-
Kanatrol	Lusofarmaco	Italy	-
Kanescin	Torlan	Spain	-
Kano	Pierrel	Italy	-
Keimicina	Robin	Italy	-
Koptin	Chinoin	Mexico	-
Ophtalmokal ixan	Bristol	France	-
Orakanamicil	Merifarma	Italy	-
Otokal ixan	Bristol	France	-
Visiokan	S.I.F.I.	Italy	-

Raw Materials

Bacterium S. Kanamyceticus
Soybean meal
Dextrin

Manufacturing Process

As described in US Patent 2,931,798, Streptomyces kanamyceticus (K2-J) was first cultured in shake flasks in the following media: (a) 0.75% meat extract, 0.75% peptone, 0.3% NaCl, with 1.0% of starch, dextrin, maltose, glucose, lactose, sucrose or glycerol; or (b) 2.0% soybean meal, 0.05% KCl, 0.05% $MgSO_4 \cdot 7H_2O$, 0.5% NaCl, 0.2% $NaNO_3$, with 1.0% of starch, dextrin, maltose, glucose, lactose, sucrose or glycerol. The initial pH of all media was adjusted to 7.0. After 24 to 48 hours shaking in some cases the pH decreased to about 6.0 to 6.8, but from 72 to 120 hours the pH rose and became 7.5 to 8.6. The production of kanamycin was apparent after 48 hours and, depending on the media; the maximum production was found after 72 to 120 hours.

The yield was highest with starch or dextrin, intermediate and about the same with sucrose, glucose, maltose and lactose and poorest with glycerol. Kanamycin was produced by media containing soybean meal, peanut meal, cottonseed meal, corn steep liquor, peptone, yeast extract or meat extract, with or without sodium nitrate. Commercially available soybean meal was recognized to be one of the best nitrogen sources. The addition of corn steep liquor, peptone, yeast extract or nitrate to the soybean meal promoted the production of kanamycin.

The brownish white kanamycin (5 g) was dissolved in 50 ml of 60% aqueous methanol, insoluble material was removed and to the filtrate 40 ml of 60% aqueous methanol containing 2,000 mg of ammonium sulfate was added, and the precipitated kanamycin sulfate was collected, washed with 50 ml of 80% aqueous methanol, and dried. Thus, 4.5 g of kanamycin sulfate was obtained as a light brownish powder.

References

Merck Index 5118
Kleeman and Engel p. 508
PDR p. 698
I.N.p.539
REM p. 1181
Umezawa, H., Maeda, K. and Ueda, M.; US Patent 2,931,798; April 5, 1960
Extraction:
Johnson, D.A., Hardcastle, G.A., Jr. and Perron, Y.G.; US Patent 2,936,307; May 10, 1960; assigned to Bristol-Myers Company
Purification:
Johnson, D.A. and Harcastle, G.A., Jr.; US Patent 2,967,177; January 3, 1961; assigned to Bristol-Myers Company
Separation Process:
Rothrock, J.W. and Putter, I.; US Patent 3,032,547; May 1, 1962; assigned to Merck and Co.,Inc.

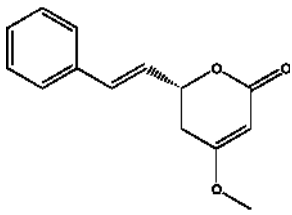
KAWAIN

Therapeutic Function: Anesthetic; Tranquilizer

Chemical Name: (R-(E))-5,6-Dihydro-4-methoxy-6-styryl-2H-pyran-2-one

Common Name: Cavain; Gonosan; Kavain; Kava pyrone; Kawain

Structural Formula:



Chemical Abstracts Registry No.: 500-64-1

Trade Name	Manufacturer	Country	Year Introduced
Largon	Klinge	-	-

Raw Materials

Ethyl acetoacetate
Bromosuccinimide
Zinc

Manufacturing Process

To 1170 g ethyl acetoacetate at 100-110°C was added a little at time 1605 g bromosuccinimide. After cooling to the mixture was added 300 ml of carbon tetrachloride. From the mixture was isolated ethyl ester of bromoacetoacetic acid which was distilled at 105-125°C/18 mm; yield 67%.

By condensation of the mixture 1400 g ethyl ester of bromoacetoacetic acid, 700 g bromosuccineimide, 500 ml benzene and 350 mg zinc was prepared (R)-5,6-dihydro-4-methoxy-6-styryl-2H-pyran-2-one; melting point 157°C, yield 60-70%.

References

Fr. Brevet D'Invention 1,526,596; June 9, 1967; Assigned to Spezialchemie G.m.b.H and Co. Residant en Republique Federale d'Allemgane

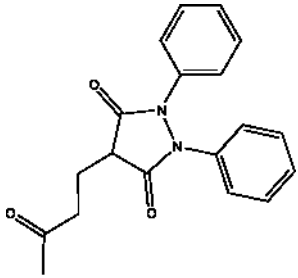
KEBUZONE

Therapeutic Function: Antirheumatic

Chemical Name: 4-(3-Oxobutyl)-1,2-diphenyl-3,5-pyrazolidinedione

Common Name: Ketophenylbutazone

Structural Formula:



Chemical Abstracts Registry No.: 853-34-9

Trade Name	Manufacturer	Country	Year Introduced
Chebutan	Bioindustria	Italy	1961
Phloguron	Steiner	W. Germany	1976
Chetazolidine	Zeria	Japan	-
Chetopir	Sidus	Italy	-
Chetosol	Aristochimica	Italy	-
Copirene	Marxer	Italy	-
Ejor	Elea	Argentina	-
Hichillos	Kotani	Japan	-
Kebuzon	Steiner	W. Germany	-
Kentan-S	Sawai	Japan	-
Ketazon	Kyowa	Japan	-
Ketazone	Spofa	Czechoslovakia	-
Ketobutan	Santen	Japan	-
Ketobutane	Yamagata	Japan	-
Ketobutazone	Toho	Japan	-
Ketofen	Francia	Italy	-
Ketophezon	Kissei Pharmaceutical Co., Ltd.	Japan	-
Neo-Panalgyl	Italsuisse	Italy	-
Neuphenyl	Ohta	Japan	-
Pecnon	Sanken	Japan	-
Reumo Campil	Lopez-Brea	Spain	-
Vintop	Maruro	Japan	-

Raw Materials

Diethyl malonate
Hydrazobenzene
Sodium ethoxide
Ethylene glycol
Methyl vinyl ketone
Acetone

Manufacturing Process

(a) 3,3-ethylene dioxyburyl malonic acid diethyl ester: Diethylmalonate is reacted with methyl vinyl ketone and the resulting oxobutyl diethylmalonate is reacted with ethylene glycol.

(b) 1,2-diphenyl-4-(3',3'-ethylene dioxybutyl)3,5-dioxopyrazolidine: 274 parts of (3,3-ethylene dioxybutyl)-malonic acid diethyl ester are dissolved in 100 parts by volume of abs. benzene and 57 parts of sodium ethylate and 184 parts of hydrazobenzene are added. Heat is generated. The reaction mass is boiled for 15 hours under reflux. After cooling, it is poured into water, separated and the aqueous part is washed twice with benzene. The benzene solutions are washed three times with 2N sodium carbonate solution and the unified aqueous solutions are acidified with 2N hydrochloric acid. The 1,2-phenyl-4-(3',3'-ethylene dioxybutyl)-3,5-dioxopyrazolidine which precipitates can be recrystallized from alcohol. Melting point 165°C to 167°C.

(c) 1,2-diphenyl-4-(3'-oxobutyl)-3,5-dioxopyrazolidine: 36.6 parts of 1,2-diphenyl-4-(3',3'-ethylene dioxybutyl)-3,5-dioxopyrazolidine in 750 parts by

volume of acetone are boiled under reflux for 18 hours with 0.35 part of p-toluene sulfonic acid. The solution is then filtered, 1,500 parts of water are added and the whole is allowed to stand for 24 hours at 5°C. The 1,2-diphenyl-4-(3'-oxobutyl)-3,5-dioxopyrazolidine which precipitates is filtered off under suction and washed with 50% acetone. Melting point from alcohol/water mixture: 115.5°C to 116.5°C. Sometimes a crystal form is obtained which melts at 127.5°C to 128.5°C.

References

Merck Index 5125
Kleeman and Engel p. 509
I.N. p. 540
Denss, R., Pfister, R.and Hafliger, F.; US Patent 2910,481; October 27, 1959; assiged to Geigy Chemical Corp.

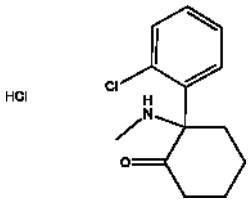
KETAMINE HYDROCHLORIDE

Therapeutic Function: Anesthetic

Chemical Name: 2-(o-Chlorophenyl)-2-(methylamino)-cyclohexanone hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1867-66-9; 6740-88-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ketanest	Parke Davis	W. Germany	1969
Ketanest	Parke Davis	UK	1970
Ketalar	Parke Davis	US	1970
Ketalar	Sankyo	Japan	1970
Ketalar	Parke Davis	France	1970
Ketaject	Bristol	US	1970
Ketalar	Parke Davis	Italy	1972

Raw Materials

Cyclopentyl bromide
Methylamine
Bromine
o-Chlorobenzonitrile
Magnesium

Manufacturing Process

The 1-hydroxycyclopentyl-(o-chlorophenyl)-ketone N-methylimine used as an intermediate is prepared as follows. To the Grignard reagent prepared from 119.0 g of cyclopentyl bromide and 19.4 g of magnesium is added 55.2 g of o-chlorobenzonitrile. The reaction mixture is stirred for 3 days and thereafter hydrolyzed in the usual manner. From the hydrolysis there is obtained o-chlorophenylcyclopentylketone, BP 96° to 97°C (0.3 mm), n_D^{25}1.5452. To 21.0 g of the ketone is added 10.0 g of bromine in 80 ml of carbon tetrachloride.

1-Bromocyclopentyl-(o-chlorophenyl)-ketone, BP 111° to 114°C (0.1 mm) is isolated in the usual manner. Since it is unstable, it must be used immediately. The bromoketone (29.0 g) is dissolved in 50 ml of liquid methylamine. After one hour, the excess liquid methylamine is allowed to evaporate. The organic residue is dissolved in pentane, and upon evaporation of the solvent, 1-hydroxycyclopentyl-(o-chlorophenyl)-ketone N-methylimine, MP 62°C, is isolated.

1-Hydroxycyclopentyl-(o-chlorophenyl)-ketone N-methylimine (2.0 g) is dissolved in 15 ml of Decalin and refluxed for 2,5 hours. After evaporation of the Decalin under reduced pressure, the residue is extracted with dilute hydrochloric acid, the solution treated with decolorizing charcoal, and the resulting acidic solution is made basic. The liberated product, 2-methylamino-2-(o-chlorophenyl)-cyclohexanone, after crystallization from pentane-ether, has MP 92° to 93°C. The hydrochloride of this compound has MP 262° to 263°C.

References

Merck Index 5133
Kleeman and Engel p. 510
PDR p. 1356
OCDSVol.1 p.57 (1977) and 2, 16 (1980)
DOT 2 (4) 152 (1966); 6 (2) 42 (1970) and 2,16 (1980)
I.N. p. 542
REM p. 1045
Stevens, C.L.; US Patent 3,254,124; May 31, 1966; assigned to Parke, Davis and Company

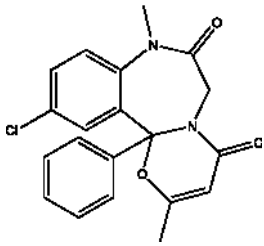
KETAZOLAM

Therapeutic Function: Antianxiety

Chemical Name: 11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]-oxazino-[3,2-d][1,4]benzodiazepine-4,7-(6H)-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 27223-35-4

Trade Name	Manufacturer	Country	Year Introduced
Anxon	Beecham	UK	1980
Solatran	Beecham	Switz.	1980
Solatran	Beecham	W. Germany	1980
Unakalm	Upjohn	France	1981
Ansietin	Exa	Argentina	-
Contamex	Beecham-Wulfing	W. Germany	-
Loftran	Beecham	-	-

Raw Materials

2-(2-Amino-N-methylacetamido)-5-chlorobenzophenone
Diketene

Manufacturing Process

A solution of 0.7 g of 2-(2-amino-N-methylacetamido)-5-chlorobenzophenone in 10 ml of a 50% solution (by weight) of diketene in acetone is refluxed for 3 hours and then evaporated to give a brown oil. The oil is chromatographed on 200 g of silica gel using a 1:1 (by volume) mixture of ethyl acetate cyclohexane; 25 ml fractions are collected. Fractions 11-14 are combined, mixed with chloroform, evaporated and triturated with ether to give 0.337 g of 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1.4] benzodiazepine-4,7(6H)-dione as a pale yellow solid, MP 174°C to 176°C.

References

Merck Index 5134
DFU 1 (6) 293 (1976)

OCDS Vol. 1 p. 369 (1977)
DOT 16 (9) 293 (1980)
I.N. p. 542
Szmuszkoviez, J.; US Patent 3,575965; April 20, 1971; assigned to The Upjohn Co.

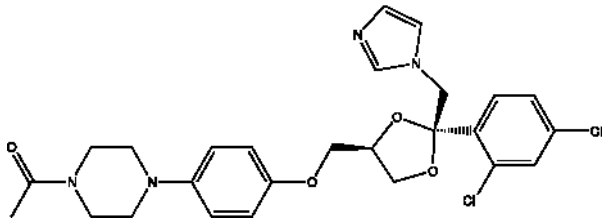
KETOCONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 65277-42-1

Trade Name	Manufacturer	Country	Year Introduced
Nizoral	Janssen	US	1981
Nizoral	Janssen	W. Germany	1981
Nizoral	Janaen	Switz.	1981
Nizoral	Janssen	UK	1981
Nizoral	Janssen-Le Brun	France	1983
Nizoral	Janssen	Italy	1983
Ketazol	Exa	Argentina	-

Raw Materials

4-(1-Piperazinyl)phenol dihydrobromide
Acetic anhydride
cis-2-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl methyl methane sulfonate

Manufacturing Process

(A) A mixture of 33.8 parts of 4-(4-piperazinyl)phenol dihydrobromide, 11.2 parts of acetic acid anhydride, 42 parts of potassium carbonate and 300 parts

of 1,4-dioxane is stirred and refluxed for 3 days. The reaction mixture is filtered and the filtrate is evaporated. The solid residue is stirred in water and sodium hydrogen carbonate is added. The whole is stirred for 30 minutes. The precipitated product is filtered off and dissolved in a diluted hydrochloric acid solution. The solution is extracted with trichloromethane. The acid aqueous phase is separated and neutralized with ammonium hydroxide. The product is filtered off and crystallized from ethanol, yielding 5.7 parts of 1-acetyl-4-(4-hydroxyphenyl)piperazine; MP 181-183°C.

(B) A mixture of 2.4 parts of 1-acetyl-4-(4-hydroxyphenyl)piperazine, 0.4 part of sodium hydride dispersion 78%; 75 parts of dimethylsulfoxide and 22.5 parts of benzene is stirred for one hour at 40°C. Then there are added 4.2 parts of cis-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl methane sulfonate and stirring is continued overnight at 100°C. The reaction mixture is cooled and diluted with water. The product is extracted with 1,1'-oxybisethane. The extract is dried, filtered and evaporated. The residue is crystallized from 4-methyl-2-pentanone. The product is filtered off and dried, yielding 3.2 parts (59%) of cis-1-acetyl-4-[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxyl phenyl]piperazine; MP 146°C.

References

Merck Index 5139
DFU 4 (7) 496 (1979)
PDR p. 956
OCDS Vol. 3 p. 132 (1984)
DOT 17 (9) 377 (1981)
I.N. p. 542
REM p. 1229
Heeres, J., Backx, L.J.J. and Mostmans, J.H.; US Patent 4,144,346; March 13,1979; assigned to Janssen Pharmaceutica N.V. (Belgium)

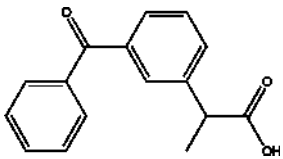
KETOPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: m-Benzoylhydratropic acid

Common Name: 2-(3-Benzoyiphenyl)propionic acid

Structural Formula:



Chemical Abstracts Registry No.: 22071-15-4

Trade Name	Manufacturer	Country	Year Introduced
Profenid	Specia	France	1973
Orudis	May and Baker	UK	1973
Alrheumin	Bayropharm	W. Germany	1975
Orudis	Farmitalia	Italy	1975
Keto	Sigurta	Italy	1976
Orudis	Hokuriku	Japan	1978
Capisten	Kissei Pharmaceutical Co., Ltd.	Japan	1978
Inflen	Ohta	Japan	1983
Zaditen	Sandoz	Japan	1983
Orudis	Leo Rhodia	Sweden	1983
Alrheumat	Bayer	UK	-
Arcental	Janovich	Spain	-
Dexal	Pulitzer	Italy	-
Fastum	Manetti-Roberts	Italy	-
Flexen	Italfarmaco	Italy	-
Helenil	Roux-Ocefa	Argentina	-
Iso-K	San Carlo	Italy	-
Kefenid	S.I.T.	Italy	-
Ketalgin	I.B.P.	Italy	-
Ketofen	Nobel	Turkey	-
Keton	Ilsan	Turkey	-
Ketonal	Lek	Yugoslavia	-
Ketopron	Biosintetica	Brazil	-
Ketoprosil	Liberman	Spain	-
Ketoval	Valles Mestre	Spain	-
Kevadon	Lemonier	Argentina	-
Knavon	Belupo Ltd.	Yugoslavia	-
Lertus	Exa	Argentina	-
Meprofen	A.G.I.P.S.	Italy	-
Niflam	Alkaloid	Yugoslavia	-
Profenid	Specia	France	-
Remauric	Lifepharma	Spain	-
Romin	Fako	Turkey	-
Salient	Biomedica Foscama	Italy	-
Sinketol	Italchemie	Italy	-
Wasserprofen	Wassermann	Spain	-

Raw Materials

Ethanol
(3-Benzoylphenyl)acetonitrile
Sulfuric acid
Sodium
Methyl iodide

Manufacturing Process

In an initial step, the sodium derivative of ethyl (3-benzoylphenyl) cyanoacetate is prepared as follows: (3-benzoylphenyl)acetonitrile (170 9) is dissolved in ethyl carbonate (900 g). There is added, over a period of 2 hours, a sodium ethoxide solution [prepared from sodium (17.7 g) and anhydrous ethanol (400 cc)], the reaction mixture being heated at about 105° to 115°C and ethanol being continuously distilled. A product precipitates. Toluene (500 cc) is added, and then, after distillation of 50 cc of toluene, the product is allowed to cool. Diethyl ether (600 cc) is added and the mixture is stirred for 1 hour. The crystals which form are filtered off and washed with diethyl ether (600 cc) to give the sodium derivative of ethyl (3-benzoylphenyl)cyanoacetate (131 g).

Then, ethyl methyl(3-benzoylphenyl)cyanoacetate employed as an intermediate material is prepared as follows: The sodium derivative of ethyl (3-benzoylphenyl)cyanoacetate (131 g) is dissolved in anhydrous ethanol (2 liters). Methyl iodide (236 g) is added and the mixture is heated under reflux for 22 hours, and then concentrated to dryness under reduced pressure (10 mm Hg). The residue is taken up in methylene chloride (900 cc) and water (500 cc) and acidified with 4N hydrochloric acid (10 cc). The methylene chloride solution is decanted, washed with water (400 cc) and dried over anhydrous sodium sulfate. The methylene chloride solution is filtered through a column containing alumina (1,500 g). Elution is effected with methylene chloride (6 liters), and the solvent is evaporated under reduced pressure (10 mm Hg) to give ethyl methyl(3-benzoylphenyl)cyanoacetate (48 g) in the form of an oil.

In the final production preparation, a mixture of ethyl methyl(3-benzoylphenyl)cyanoacetate (48 g), concentrated sulfuric acid (125 cc) and water (125 cc) is heated under reflux under nitrogen for 4 hours, and water (180 cc) is then added. The reaction mixture is extracted with diethyl ether (300 cc) and the ethereal solution is extracted with N sodium hydroxide (300 cc). The alkaline solution is treated with decolorizing charcoal (2 g) and then acidified with concentrated hydrochloric acid (40 cc). An oil separates out, which is extracted with methylene chloride (450 cc), washed with water (100 cc) and dried over anhydrous sodium sulfate. The product is concentrated to dryness under reduced pressure (20 mm Hg) to give a brown oil (33.8 g).

This oil is dissolved in benzene (100 cc) and chromatographed through silica (430 g). After elution with ethyl acetate, there is collected a fraction of 21 liters, which is concentrated to dryness under reduced pressure (20 mm Hg). The crystalline residue (32.5 g) is recrystallized from acetonitrile (100 cc) and a product (16.4 g), MP 94°C, is obtained. On recrystallization from a mixture of benzene (60 cc) and petroleum ether (200 cc), there is finally obtained 2-(3-benzoylphenyl)propionic acid (13.5 g), MP 94°C.

References

Merck Index 5142
Kleeman and Engel p. 511
OCDS Vol. 2 p. 64 (1980)
DOT 9 (11) 469 (1973) and 19 (3) 160 (1983)
I.N. p. 543

Farge, D., Messer, M.N. and Moutonnier, C.; USPatent 3,641,127; February 8,1972; assigned to RhonePoulenc S.A., France

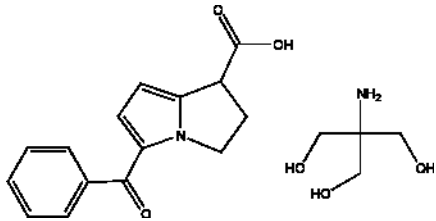
KETOROLAC TROMETHAMINE

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: 1H-Pyrrolizine-1-carboxylic acid, 2,3-dihydro-5-benzoyl-, (+-)-, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Common Name: Ketorolac tromethamine; Ketorolac trometamol; Trometamol keterolac

Structural Formula:



Chemical Abstracts Registry No.: 74103-07-4

Trade Name	Manufacturer	Country	Year Introduced
Acular	Allergan	India	-
Apo-Ketorolac Ophthalmic Solution	Apotex Inc.	-	-
Ketorolac Tromethamine Injection USP	Sabex Inc.	Canada	-
Toradol	Syntex	Switz.	-
Toradol	Roche	-	-
Toradol	Apotex Inc.	Canada	-
Toradol	Novopharm	Canada	-
Toradol	Nu-Pharm Inc.	Canada	-
Toradol	Ratiopharm	Canada	-

Raw Materials

Bromine
Methylaniline
Triethylamine
Butyl diglyme
Pyrrole
Diglyme
Sodium hydroxide
4-Chlorobutanoyl chloride
Phosphorus tribromide
Methyl magnesium chloride
ALIQUAT (phase transfer catalyst)
Phosphorus oxychloride
Benzoyl chloride

Manufacturing Process

Preparation of 2-bromo-4-chloro-N-methyl-N-phenylbutanamide.

4-Chlorobutanoyl chloride (62 g, 440 mmol) and phosphorus tribromide (3 g) were added to a distillation flask, and heated to 90°C. Bromine (77.5 g, 485 mmol) was added over eight hours, with the solution being allowed to decolorize between additions. After the addition was complete, and the solution decolorized, a vacuum was slowly applied, and the acid gases and phosphorus tribromide scrubbed. Unreacted starting material was distilled at 98-100°C/22 mm Hg, and the temperature slowly increased to 105°C, where a mixture of 2-bromo-4-chlorobutanoyl chloride and 2-bromo-4-chlorobutanoyl bromide began to distill. Pure 2-bromo-4-chlorobutanoyl bromide distilled at approximately 108°C. The combined yield of 2-bromo-4-chlorobutanoyl chloride and 2-bromo-4-chlorobutanoyl bromide was 100.5 g, with a bromide/chloride ratio of approximately 6:1. The mixture of 2-bromo-4-chlorobutanoyl bromide and chloride is directly usable in the preparation of the butanamide, if desired, or may be separated and either component used.

2-Bromo-4-chlorobutanoyl bromide (300 mmol) was added to a solution of N-methylaniline (320 mmol) and triethylamine (330 mmol) in toluene (340 mL). The reaction was exothermic, and the mixture was cooled to maintain the temperature at about 40°C. After the addition was complete, the resulting mixture was stirred for 30 minutes, 150 mL water was added, and the mixture was stirred further. The aqueous and organic phases were separated, and the organic phase was washed with 5% hydrochloric acid and with water. The toluene was evaporated completely under vacuum to yield 86.3 g 2-bromo-4-chloro-N-methyl-N-phenylbutanamide (98% yield, approximately 95-96% pure).

A solution of methylmagnesium chloride in butyl diglyme (4.0 L, 2.8 M, 11.2 mol, 2.8 equivalents with respect to 2-bromo-4-chloro-N-methyl-N-phenylbutanamide) was added to a 12 L 4-necked round bottom flask fitted with a mechanical stirrer and two 1 L addition funnels, under a nitrogen atmosphere. 2-Bromo-4-chloro-N-methyl-N-phenyl-butanamide (3.98 mol) was added to the first addition flask, and pyrrole (3.04 equivalents with respect to 2-bromo-4-chloro-N-methyl-N-phenyl-butanamide) was added to the second. The pyrrole was slowly added to the methylmagnesium chloride/butyl diglyme solution at 45-50°C over 3 hours. The resulting viscous mixture was cooled to 25°C and stirred for 30 min. 2-Bromo-4-chloro-N-methyl-N-phenylbutanamide was added to the resulting mixture over a period of 2 hours at 25-30°C, and the resulting solution was stirred for another 3 hours.

The dark colored reaction mixture was transferred into 5.76 mol 2 N hydrochloric acid with rapid stirring for 1 hour. The aqueous phase was removed, and 0.8 L 15 weight % ammonium chloride in water was added to the organic phase. The resulting mixture was stirred at 35-40°C for 10 min, the aqueous phase then removed, and hexanes (2.4 L) added. The resulting suspension was cooled to -20°C and maintained at that temperature for a few minutes. The precipitate was filtered in a 300 mL sintered glass funnel and washed with hexanes (1 L). Drying of the solid under vacuum at 25-30°C yielded 4-chloro-N-methyl-N-phenyl-2-(2-pyrrolyl)butanamide (81% yield).

A solution of 4-chloro-N-methyl-N-phenyl-2-(2-pyrrolyl)butanamide in toluene was added dropwise at 85°C over 40 min to 1 hour to a stirred suspension of ALIQUAT 336 (phase transfer catalyst, 2 mol % with respect to pyrrolylbutanamide) and granular sodium hydroxide (3 equivalents) in toluene (50 mL). After the addition was complete, the suspension was stirred under a nitrogen atmosphere at a temperature of 85°C for 30 min, then cooled to 35°C. Cooled water (200 mL) was rapidly added to the mixture and stirred for 15 min at 25°C. The solution was rinsed with water and the layers were separated. The organic layer was washed with water, then distilled under atmospheric pressure to recover the toluene and water. The resultant solution was cooled to 50°C and allowed to crystallize after the addition of hexane and a seed crystal. The suspension was cooled to 5°C and stirred for 15 minutes. The resultant precipitate was filtered, washed with 100 mL of hexane, and dried under vacuum at 25°C to yield approximately 38 g (63%) N-methyl-N-phenyl-2,3-dihydro-1H-pyrrolizine-1-carboxamide. This solid was recrystallized from toluene to yield colorless crystals of N-methyl-N-phenyl-2,3-dihydro-1H-pyrrolizine-1-carboxamide, melting point 112-112.5°C.

Benzoyl chloride (4.3 mol) was added dropwise to a rapidly stirring mixture of piperidine (4.3 mol), sodium hydroxide (4.7 mol), toluene (1 L), and water (1.7 L) over a period of 70 min. After the addition was complete, the mixture was stirred at 25°C for one hour. The organic and aqueous phases were separated, and the organic phase was washed with 2 N hydrochloric acid, concentrated by rotary evaporation, and distilled under vacuum to yield benzoylpiperidine as a colorless liquid which crystallized on standing (95% yield, boiling point 169-171°C).

N-Methyl-N-phenyl-2,3-dihydro-1H-pyrrolizine-1-carboxamide (480 mmol) and toluene (100 mL) were added to a mixture of benzoylpiperidine (1.05 eq.) and phosphorus oxychloride (0.96 eq.), which had been stirred at 25°C for 1 hour. An additional 100 mL toluene was added. The suspension was heated to at 40-45°C for 4 hours. The resulting syrup was transferred into a rapidly stirring solution of sodium hydroxide (4.5 mol), piperidine (1.0 mL), and water (650 mL) at 25-35°C and the mixture was stirred for 1 hour. A mixture of toluene (100 mL), water (50 mL), and sodium hydroxide (12 g, 300 mmol) was added to the reaction flask, and the reaction mixture was stirred at 25°C for 1 hour. The suspension was then heated to 75°C and the layers were separated. The organic layer was cooled to 60°C and hexane (100 mL) was slowly added, and the solution slowly stirred and cooled to -15°C. The precipitate was filtered, washed with toluene/hexane (2:1) and then with hexane, and dried under vacuum at 25°C to yield 5-benzoyl-N-methyl-N-phenyl-2,3-dihydro-1H-pyrrolizine-1-carboxamide (83.5% yield).

Preparation of ketorolac tromethamine.

A mixture of 34.4 g (100 mmol) 5-benzoyl-N-methyl-N-phenyl-2,3-dihydro-1H-pyrrolizine-1-carboxamide, 25 g sodium hydroxide in 25 mL water, and 80 mL methanol was refluxed for 5 hours. The mixture was cooled to room temperature, stirred under nitrogen for sixteen hours, and then diluted with 80 mL of water. The mixture was extracted with toluene, and the aqueous and organic phases were separated. The aqueous phase was acidified with 6 N hydrochloric acid. The resulting precipitate was extracted with dichloromethane. The combined extract was treated with activated clay decolorizing agent (4.5 g) for 30 minutes, filtered, and concentrated by

atmospheric distillation. Hexane was added and the mixture allowed to cool to 0-5°C. The product, 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid (ketorolac) was collected by filtration, washed with 100 mL of hexane/dichloromethane (7:3), and dried at 60°C under vacuum, to yield ketorolac (83.4% yield), melting point 152-162°C. Ketorolac (25 g) and 11.9 g tromethamine were dissolved in 175 mL methanol. The solution was filtered and the filter washed with 40 mL methanol. The resulting solution was concentrated by vacuum distillation. Ethylacetate was added to precipitate the ketorolac tromethamine; and the solution was cooled to room temperature for two hours, cooled further to 0°C, and filtered. The precipitate was washed with ethyl acetate/methanol (4:1) and dried under vacuum at a temperature of 65°C, to yield ketorolac tromethamine (95% yield).

References

Yarrington P.J. et al.; US Patent No. 6,197,976; 03.06.2001; Assigned to Syntex (U.S.A.) LLC

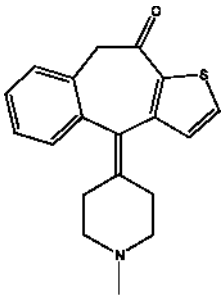
KETOTIFEN

Therapeutic Function: Anti-asthmatic, Antihistaminic

Chemical Name: 4-(1-Methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta [1,2-b]-thiophen-10(9H)-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34580-13-7

Raw Materials

4-Chloro-1-methylpiperidine
Magnesium
10-Methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one
Hydrogen chloride

Trade Name	Manufacturer	Country	Year Introduced
Zaditen	Wander	Switz.	1978
Zaditen	Sandoz	W. Germany	1979
Zaditen	Sandoz	UK	1979
Zaditen	Sandoz	France	1980
Zaditen	Sandoz	Italy	1982
Zaditen	Sandoz	Japan	1983
Totifen	Chiesi	Italy	1983
Zasten	Sandoz	-	-

Manufacturing Process

3.07 g of iodine-activated magnesium shavings are covered with a layer of 25 cc of tetrahydrofuran, and approximately 1/10 of a solution of 17.7 g of 4-chloro-1-methylpiperidine base in 70 cc of absolute tetrahydrofuran is added. The Grignard reaction is initiated by the addition of a few drops of 1,2-dibromoethane. The remaining 4-chloro-1-methylpiperidine solution is then added dropwise to the magnesium at such a rate that the reaction mixture boils continuously at reflux without external heating. Boiling at reflux is then continued for 1 hour. 15.3 g of 10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one are subsequently added portionwise at 20°C, within 40 minutes, with slight cooling. After stirring at 20°C for 1,5 hours, the reaction solution is poured on a mixture of 180 g of ice and 20 g of ammonium chloride. The free base is extracted with chloroform.

The chloroform solution is concentrated and the residue recrystallized from 270 cc of absolute ethanol. The pure 10-methoxy-4-(1-methyl-4-piperidyl)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ol base, having a melting point of 194°C to 196°C, is obtained in this manner. Microanalysis corresponds with the formula $C_{20}H_{23}NO_2S$.

A mixture of 3.4 g of 10-methoxy-4-(1-methyl-4-piperidyl)-4H-benzo[4,5] cyclohepta [1,2-b]thiophen-4-ol base and 40 cc of 3N hydrochloric acid is kept in a boiling water bath at 95°C to 100°C for 1 hour. The mixture is subsequently made alkaline with concentrated caustic soda solution at 20°C while cooling, and the free base is extracted with chloroform. The chloroform solution is concentrated, and the residue is recrystallized from ethanol/water 1:1. The pure 4-(1-methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta [1,2-b] thiophen-10(9H)-one base, having a melting point of 152°C to 153°C, is obtained in this manner.

References

Merck Index 5144
DFU 2 (2) 108 (1977)
Kleeman and Engel p. 512
OCDS Vol. 3 p. 239 (1984)
DOT 14 (8) 370 (1978)
I.N. p. 543
Bourquin, J.P., Schwarb, G. and Waldvogel, E.; US Patents 3,682,930; Aug. 8, 1972; 3,770,728; Nov. 6, 1973 and 3,960,894; June 1, 1976; all assigned to Sandoz, Ltd.