K

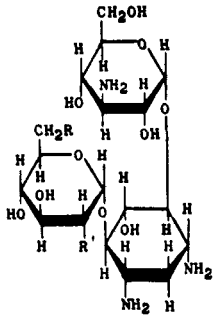
KANAMYCIN SULFATE

Therapeutic Function: Antibacterial

Chemical Name: 0-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-0-[6-amino-6-deoxy-α-D-glucopyranosyl-(1→4)-2-deoxy-D-streptamine sulfate

Common Name: —

Structural Formula:



kanosamin

deoxystreptamine

(base)

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

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

Trade Name	Manufacturer	Country	Year Introduced
Kanatrol	Lusofarmaco	Italy	–
Kanescin	Torlan	Spain	–
Kano	Pierrel	Italy	–
Keimicina	Robin	Italy	–
Koptin	Chinoin	Mexico	–
Ophtalmokalixan	Bristol	France	–
Orakanamicil	Merifarma	Italy	–
Otokalixan	Bristol	France	–
Visiokan	S.I.F.I.	Italy	–

Raw Materials

Bacterium *Streptomyces kanamyceticus*
Soybean meal
Dextrin

Manufacturing Process

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

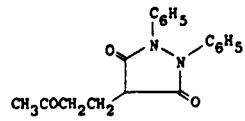
KEBUZONE

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	Japan	—
Neo-Panalgyl	Italsuisse	Italy	—
Neuphenyl	Ohta	Japan	—
Pecnon	Sanken	Japan	—
Reumo Campil	Lopez-Brea	Spain	—
Vintop	Maruro	Japan	—

Raw Materials

Diethyl malonate
Ethylene glycol
Hydrazobenzene
Methyl vinyl ketone
Sodium ethoxide
Acetone

Manufacturing Process

(a) 3,3-ethylene dioxybutyl 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 so-

lutions 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 & Engel p. 509
I.N. p. 540
Denss, R., Pfister, R. and Hafliger, F.; U.S. Patent 2,910,481; October 27, 1959; assiged to Geigy Chemical Corp.

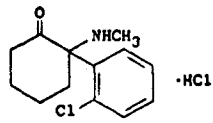
KETAMINE HYDROCHLORIDE

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	U.K.	1970
Ketalar	Parke Davis	U.S.	1970
Ketalar	Sankyo	Japan	1970
Ketalar	Parke Davis	France	1970
Ketaject	Bristol	U.S.	1970
Ketalar	Parke Davis	Italy	1972

Raw Materials

Cyclopentyl bromide
o-Chlorobenzonitrile
Methylamine
Magnesium
Bromine

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 2½ 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 & Engel p. 510
PDR p. 1356
OCDS Vol. 1 p. 57 (1977) & 2, 16 (1980)
DOT 2 (4) 152 (1966); 6 (2) 42 (1970) & 2, 16 (1980)
I.N. p. 542
REM p. 1045
Stevens, C.L.; U.S. Patent 3,254,124; May 31, 1966; assigned to Parke, Davis and Company

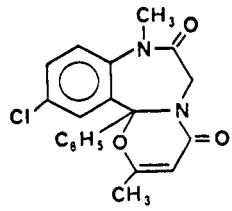
KETAZOLAM

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	U.K.	1980
Solatran	Beecham	Switz.	1980
Solatran	Beecham	W. Germany	1980

Trade Name	Manufacturer	Country	Year Introduced
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.; U.S. Patent 3,575,965; April 20, 1971; assigned to The Upjohn Co.

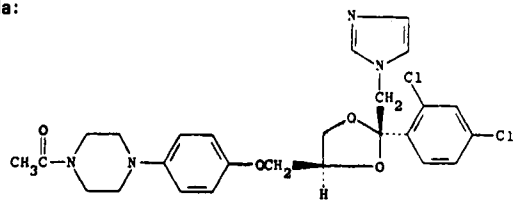
KETOCONAZOLE

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	U.S.	1981
Nizoral	Janssen	W. Germany	1981
Nizoral	Janssen	Switz.	1981

Trade Name	Manufacturer	Country	Year Introduced
Nizoral	Janssen	U.K.	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-(1-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 181.3°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-ylmethoxy]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.; U.S. Patent 4,144,346; March 13, 1979; assigned to Janssen Pharmaceutica N.V. (Belgium)

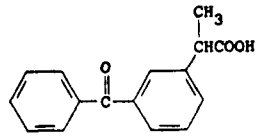
KETOPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: m-benzoylhydratropic acid

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

Structural Formula:



Chemical Abstracts Registry No.: 22071-15-4

Trade Name	Manufacturer	Country	Year Introduced
Profenid	Specia	France	1973
Orudis	May & Baker	U.K.	1973
Alrheumin	Bayropharm	W. Germany	1975
Orudis	Farmitalia	Italy	1975
Keto	Sigurta	Italy	1976
Orudis	Hokuriku	Japan	1978
Capisten	Kissei	Japan	1978
Inflen	Ohta	Japan	1983
Zaditen	Sandoz	Japan	1983
Orudis	Leo Rhodia	Sweden	1983
Alrheumat	Bayer	U.K.	–
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	Yugoslavia	–
Lertus	Exa	Argentina	–
Meprofen	A.G.I.P.S.	Italy	–
Niflam	Alkaloid	Yugoslavia	–
Profenid	Specia	France	–
Remauric	Lifepharma	Spain	–
Romin	Fako	Turkey	–
Salient	Biomedia Foscama	Italy	–
Sinketol	Italchemie	Italy	–
Wasserprofen	Wassermann	Spain	–

Raw Materials

(3-Benzoylphenyl)acetonitrile
Ethanol
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 g) 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 4 N 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 & Engel p. 511
OCDS Vol. 2 p. 64 (1980)
DOT 9 (11) 469 (1973) & 19 (3) 160 (1983)
I.N. p. 543
Farge, D., Messer, M.N. and Moutonnier, C.; U.S. Patent 3,641,127; February 8, 1972; assigned to Rhone-Poulenc S.A., France

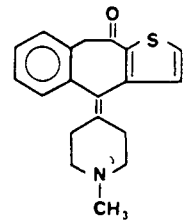
KETOTIFEN

Therapeutic Function: Antiasthmatic, 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

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

Raw Materials

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

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 1½ 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 3 N 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 & 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.; U.S. 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.