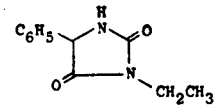
ETHOTOIN

Therapeutic Function: Anticonvulsant

Chemical Name: 3-ethyl-5-phenyl-2,4-imidazolidinedione

Common Name: 3-ethyl-5-phenylhydantoin

Structural Formula:



Chemical Abstracts Registry No.: 86-35-1

Trade Name	Manufacturer	Country	Year Introduced
Peganone	Abbott	U.S.	1957
Accenon	Dainippon	Japan	–

Raw Materials

Benzaldehyde cyanohydrin
Hydrogen chloride
Urea
Ethyl iodide

Manufacturing Process

Benzaldehyde cyanohydrin is reacted with urea to displace the hydroxyl group of the cyanohydrin. That intermediate is treated with HCl to convert the urea nitrogen to a nitrile. The resultant imine is hydrolyzed to the phenylhydantoin. Alkylation with ethyl iodide gives ethotoin, as described by A. Pinner in *Chem. Ber.* 21, 2325 (1888).

References

Merck Index 3698
Kleeman & Engel p. 374
PDR p. 546
OCDS Vol. 1 p. 245 (1977)
I.N. p. 398
REM p. 1083
Close, W.J.; U.S. Patent 2,793,157; May 21, 1957; assigned to Abbott Laboratories

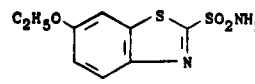
ETHOXZOLAMIDE

Therapeutic Function: Diuretic

Chemical Name: 6-ethoxy-2-benzothiazolesulfonamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 452-35-7

Trade Name	Manufacturer	Country	Year Introduced
Cardrase	Upjohn	U.S.	1957
Ethamide	Allergan	U.S.	1967
Glaucotensil	Farmila	Italy	–
Redupressin	Thilo	W. Germany	–
Poenglausil	Poen	Argentina	–

Raw Materials

6-Ethoxybenzothiazole-2-thiol
Sodium hypochlorite
Ammonia
Potassium permanganate

Manufacturing Process

Preparation of 6-Ethoxybenzothiazole-2-Sulfenamide: A solution prepared by dissolving 21.0 grams (0.1 mol) of 6-ethoxybenzothiazole-2-thiol, Sebrell and Boord, *J. Am. Chem. Soc.* 45: 2390 to 2399 (1923), in 75 ml of water containing 5 grams of sodium hydroxide, and 75 ml of 10% sodium hypochlorite solution were added simultaneously to 300 ml of concentrated ammonium hydroxide which was cooled to 0°C, and vigorously stirred. During the addition the temperature was not allowed to rise above 5°C. The resulting solid was recovered by filtration, washed thoroughly with water, and dried at room temperature under reduced pressure. There was obtained 21 grams of 6-ethoxybenzothiazole-2-sulfenamide melting at 132° to 155°C (decomposition). Recrystallization from ethyl acetate gave a product melting at 140.5° to 143°C (decomposition).

Preparation of 6-Ethoxybenzothiazole-2-Sulfonamide: A solution of 3.39 grams (0.015 mol) of the sulfenamide in 100 ml of acetone was treated dropwise, with stirring, with a solution of 3.5 grams of potassium permanganate in 100 ml of water. The temperature rose to 42°C. After stirring an additional 10 minutes the reaction mixture was filtered to remove manganese dioxide, the latter was washed with 100 ml of warm water, and the combined filtrates were concentrated under reduced pressure to remove acetone. The residual solution was treated with charcoal, filtered and acidified with concentrated hydrochloric acid. After standing in the refrigerator for 4 hours the solid sulfonamide was recovered by filtration, washed with water and dried. There was obtained 2.37 grams of 6-ethoxybenzothiazole-2-sulfonamide melting at 180° to 190°C. Recrystallization from ethyl acetate-Skellysolve B gave 1.25 grams of material melting at 188° to 190.5°C.

References

Merck Index 3704
Kleeman & Engel p. 374
OCDS Vol. 1 p. 327 (1977)
DOT 14 (5) 207 (1978)
I.N. p. 399
Korman, J.; U.S. Patent 2,868,800; January 13, 1959; assigned to The Upjohn Company

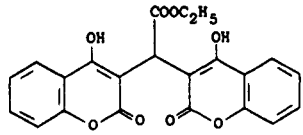
ETHYL BISCOUMACETATE

Therapeutic Function: Anticoagulant

Chemical Name: 4-Hydroxy-α-(4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-2-oxo-2H-1-benzopyran-3-acetic acid ethyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 548-00-5

Trade Name	Manufacturer	Country	Year Introduced
Tromexan	Geigy	U.S.	1950
Biscouron	Ayerst	–	–
Stabilene	Auclair	France	–

Raw Materials

Benzotetronic acid
Glyoxylic acid ethyl ester ethyl alcoholate

Manufacturing Process

7 g of benzotetronic acid are dissolved in 750 cc of water at boiling temperature and thereafter 10.5 g of glyoxylic acid ethyl ester ethyl alcoholate are added. After a short while the liquid becomes turbid and gradually a white deposit is separated. The deposit is filtrated and dried in vacuo. The melting point is 172°C to 174°C; after recrystallization from methyl alcohol 153°C to 154°C.

The crude product is dissolved in sodium lye, filtrated by means of animal charcoal precipitated by means of hydrochloric acid, and recrystallized from methyl alcohol. The melting point is 153°C to 154°C.

References

Merck Index 3719
Kleeman & Engel p. 375
I.N. p. 400
Rosicky, J.; U.S. Patent 2,482,511; September 20, 1949; assigned to Spojene Farmaceuticke Zovody (Czechoslovakia)

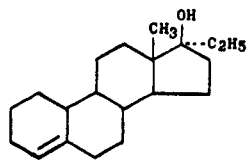
ETHYLESTRENOL

Therapeutic Function: Anabolic

Chemical Name: 19-nor-17α-pregn-4-en-17-ol

Common Name: 17α-ethyl-17β-hydroxy-19-norandrostene

Structural Formula:



Chemical Abstracts Registry No.: 965-90-2

Trade Name	Manufacturer	Country	Year Introduced
Maxibolin	Organon	U.S.	1964
Durabolin	Organon	—	—
Orabolin	Organon	U.K.	—
Orgabolin	Organon-Sankyo	Japan	—
Orgaboline	Organon	France	—

Raw Materials

17α-Ethyloestradiol-3-ethylether
Lithium
Ethylamine

Manufacturing Process

4.5 grams of lithium cut to small pieces are added to 435 ml of dry ethylamine which is cooled in ice. After the solution turns blue 9 grams of 17α-ethyloestradiol-3-ethylether dissolved in 900 ml of dry ether are added.

Subsequently, the reaction mixture is stirred at a temperature of 0° to 5°C for 20 hours, after which 50 ml of absolute ethanol are added. Then the ethylamine is distilled off at low pressure. To the remaining solution 50 ml of ether and 50 ml of water are added. The water layer is separated and extracted a few times with ether. The collected ether extracts are added to the ethereal layer, after which this ethereal solution is washed with a 2 N hydrochloric acid solution, subsequently with a saturated sodium bicarbonate solution, and then with water. The ethereal solution is then dried on sodium sulfate and finally evaporated to dryness.

The crude product is distributed between equal parts of petroleum ether and 70% methanol. From the petroleum ether layer 5.6 grams of Δ^4-17α-ethyl-17β-hydroxy-19-norandrostene with a melting point of about 50°C are obtained.

References

Merck Index 3750
Kleeman & Engel p. 375
PDR p. 1286
OCDS Vol. 1 p. 170 (1977)
I.N. p. 400
REM p. 1001
Szpilfogel, S.A. and de Winter, M.S.; U.S. Patent 2,878,267; March 17, 1959; assigned to Organon Inc.
Szpilfogel, S.A., Hanegraaf, J.A. and van Dijck, L.A.; U.S. Patent 3,112,328; Nov. 26, 1963 assigned to Organon Inc.

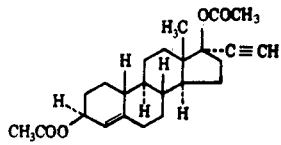
ETHYNODIOL DIACETATE

Therapeutic Function: Progestin; oral contraceptive ingredient

Chemical Name: 3β,17β-diacetoxy-17α-ethynyl-4-estrene

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 297-76-7

Trade Name	Manufacturer	Country	Year Introduced
Lutometrodiol	Searle	France	1965
Ovulen	Searle	U.S.	1966
Femulen	Searle	Italy	1971
Femulen	Searle	U.K.	1973
Alfames E	Dr. Kade	W. Germany	–
Conova	Searle	U.K.	–
Demulen	Searle	U.S.	–
Luteonorm	Seronol	Italy	–
Metrodiol	Byla	France	–
Metrulen	Searle	U.S.	–
Ovamin	Searle	U.K.	–

Raw Materials

17α-Ethynyl-19-norandrost-4-ene-3β,17β-diol (ethynodiol)
Acetic anhydride

Manufacturing Process

A mixture of 30 parts of 17α-ethynyl-19-norandrost-4-ene-3β,17β-diol, 360 parts of dry pyridine, and 111 parts of acetic anhydride, under nitrogen, is stirred and heated at the reflux temperature for about 5 hours. This reaction mixture is cooled, then poured into approximately 3,500 parts of cold water and the resulting aqueous mixture is stirred at room temperature for about 0.5 hour. The precipitate which forms is collected by filtration, then is washed on the filter with water and dried in air. This solid material is extracted into ether, and the ether solution is washed successively with 10% aqueous hydrochloric acid and 5% aqueous sodium bicarbonate.

Drying over anhydrous sodium sulfate containing decolorizing carbon followed by removal of the solvent by distillation at reduced pressure affords an oil which solidifies on standing. Recrystallization of that solid by dropwise dilution with water of a methanol solution affords 17α-ethynyl-19-norandrost-4-ene-3β,17β-diol 3,17-diacetate, melting at about 126° to 127°C.

References

Merck Index 3807
Kleeman & Engel p. 384
PDR p. 1680
OCDS Vol. 1 pp. 165, 186 (1977)
DOT 4 (1) 9 (1966)
REM p. 991
Klimstra, P.D.; U.S. Patent 3,176,013; March 30, 1965; assigned to G.D. Searle & Co.

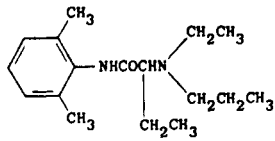
ETIDOCAINE HCl

Therapeutic Function: Local anesthetic

Chemical Name: N-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 36637-19-1; 36637-18-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Duranest	Astra	U.S.	1976
Duranest	Astra	W. Germany	1976
Duranest	Bellon	France	1977

Raw Materials

2-Bromobutyric acid
2,6-Xylidine
n-Propylamine
Hydrogen chloride
Sulfonyl chloride
Potassium iodide
Diethyl sulfate

Manufacturing Process

α-(n-Propylamino)-n-butyro-2,6-xylidide (0.243 mol) and freshly distilled diethyl sulfate (1.6 mols) were mixed in a flask equipped with reflux condenser, drying tube and stirrer. The mixture was stirred for 5 hours at 90°C. After cooling, water (110 ml) was added with stirring for 15 minutes followed by 4 M HCl (110 ml). The solution was washed with ether (3 X 100 ml) and made alkaline with 7 M NaOH to pH 10-11. The freed base was taken up in ether (3 X 100 ml); the extracts were dried over sodium sulfate, filtered and evaporated. The residue was dissolved in absolute ether (200 ml) and the hydrochloride prepared by addition of ethereal hydrogen chloride. The precipitate was filtered, washed with ether, and recrystallized twice from absolute ethanol/ether and from isopropanol/isopropylether; MP 203°C to 203.5°C; yield: 0.126 mol (52%).

The starting material is prepared by reacting 2-bromobutyric acid with sulfonyl chloride to give the acid chloride. It is then reacted with 2,6-xylidine, then with potassium iodide followed by n-propylamine.

References

Merck Index 3811
Kleeman & Engel p. 376
PDR p. 591
OCDS Vol. 2 p. 95 (1980)
I.N. p. 403
REM p. 1051
Adams, H.J.F., Kronberg, G.H. and Takman, B.H.; U.S. Patent 3,812,147; May 21, 1974; assigned to Astra Pharmaceutical Products, Inc.

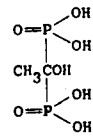
ETIDRONATE DISODIUM

Therapeutic Function: Bone calcium regulator

Chemical Name: (1-Hydroxyethylidene)bisphosphonic acid disodium salt

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 7414-83-7; 2809-21-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Etidron	Gentili	Italy	1977
Didronel	Procter & Gamble	U.S.	1978
Didronel	Gist Brocade	U.K.	1980
Didronel	Procter & Gamble	Switz.	1980
Didronel	Beytout	France	1982
Diphos	Boehr./Mann.	W. Germany	1982
Difosfen	Rubio	Spain	–
Diphosphonat	Procter & Gamble	U.S.	–

Raw Materials

Phosporous acid
Acetic anhydride
Sodium hydroxide

Manufacturing Process

Phosphorous acid was premixed with acetic acid to form a 50 wt % solution of phosphorous acid dissolved in acetic acid. The acids were mixed on a molar basis of 1.36:1, acetic acid to phosphorous acid, and this corresponded on a mol percentage basis to 57.6% acetic acid and 42.4% phosphorous acid. Acetic anhydride was continuously metered into a stream of the phosphorous acid-acetic acid mixture to form the reaction solution. The acetic anhydride was metered into the acid mixture at a mol ratio of 1.33 mols of acetic anhydride per mol of phosphorous acid. The metering rates were 18.5 lb/hr of the phosphorous acid/acetic acid premixed solution and 15.1 lb/hr acetic anhydride. The reaction solution was continuously passed through a heat exchanger where it was heated to 190°F then it was continuously fed into a two stage back-mix reaction zone where due to the heat of reaction the temperature rose to 275°F. The average residence in the reaction zone was 27 min. The reaction zone consisted of two back-mix reactors each having a capacity of 7.5 pounds of the reaction solution. A stream of reaction solution was continuously withdrawn from the second reactor and continuously mixed with a stream of water which was being metered at a rate of 2 lb/hr. This amount of water corresponded to 18% excess over the theoretical amount necessary to hydrolyze all of the acetyl-containing compounds in the reaction solution to free acids. The hydrolyzed solution was continuously passed through a heat exchanger and cooled to room temperature after which the solution was continuously passed to a crystallizer where, with agitation, the ethane-1-hydroxy-1,1-diphosphonic acid crystallized. The slurry was then filtered and the crystals were recovered and dried. Analysis of the product showed a conversion rate of phosphorous acid to ethane-1-hydroxy-1,1-diphosphonic acid of 86%. Sodium hydroxide may be used to give the disodium salt.

References

Merck Index 3812
Kleeman & Engel p. 377
PDR p. 1275
DOT 4 (3) 104 (1978)
I.N. p. 23

REM p. 979
Rogovin, L., Brawn, D.P. and Kalberg, J.N.; U.S. Patent 3,400,147; September 3, 1968; assigned to The Procter & Gamble Co.

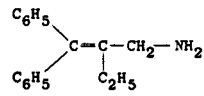
ETIFELMINE

Therapeutic Function: Central stimulant; antihypotensive

Chemical Name: 2-Diphenylmethylenebutylamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 341-00-4

Trade Name	Manufacturer	Country	Year Introduced
Etifelmine	Giulini	W. Germany	1963
Tensinase D	Chemiphar	Japan	1975
Gilutensin	Giulini	W. Germany	–

Raw Materials

2-Ethyl-3-hydroxy-3,3-diphenyl propionitrile
Hydrogen
Hydrogen chloride

Manufacturing Process

(a) Preparation of 2-ethyl-3-hydroxy-3,3-diphenyl-propylamine: 10 g of 2-ethyl-3-hydroxy-3,3-diphenyl-propionitrile are dissolved in 200 ml of methanol. 10 ml of acetic acid are added to the mixture, and the mixture is hydrogenated in the presence of platinum as catalyst. After the hydrogen uptake or consumption has ceased, the reaction is interrupted, the catalyst is filtered off and the filtrate is evaporated in vacuo to dryness. The residue is dissolved in water and, after the addition of 1 ml of hydrochloric acid, the solution extracted with ether. The acidified ether-phase is discarded. The aqueous phase is made alkaline with ammonia, whereby the base crystallizes out. The crystals are recovered and recrystallized from methanol. The melting point of the 2-ethyl-3-hydroxy-3,3-diphenyl-propylamine thereby obtained is 132°C.

(b) Preparation of 2-ethyl-3,3-diphenyl-1-amino-propene-(2)-hydrochloride: 5 g of 2-ethyl-3-hydroxy-3,3-diphenyl-propylamine are dissolved in 50 ml of acetic acid. Gaseous hydrogen chloride is passed through the solution for 10 minutes, and thereafter the solution is boiled for one hour under reflux. The solution is then distilled to dryness. The residue is dissolved in water and the acidified solution extracted with ether. The aqueous phase is separated, made alkaline with ammonia and extracted with ether. The ether phase is dried over sodium sulfate, the ether distilled off and the residue is dissolved in methanolic hydrogen chloride. On the addition of absolute ether, the hydrochloride of 2-ethyl-3,3-diphenyl-1-amino-propene-(2) is crystallized out. The crystalline substance thereby obtained has a melting point of 232°C.

References

Merck Index 3813

Kleeman & Engel p. 377
I.N. p. 403
Gebruder Giulini, G.m.b.H.; British Patent 936,041; September 4, 1963

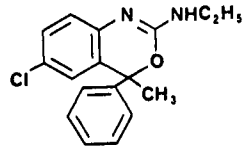
ETIFOXINE

Therapeutic Function: Tranquilizer

Chemical Name: 2-Ethylamino-4-methyl-4-phenyl-6-chloro-4H-3,1-benzoxazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 21715-46-8

Trade Name	Manufacturer	Country	Year Introduced
Stresam	Beaufour	France	1971

Raw Materials

5-Chloro-2-amino-α-methyl-α-phenylbenzyl alcohol
Ethyl mustard oil (ethyl isothiocyanate)
Mercury oxide

Manufacturing Process

(a) A solution of 50 g of 5-chloro-2-amino-α-methyl-α-phenylbenzyl alcohol in 150 ml of ether is mixed with 35 g of ethyl mustard oil and kept for 48 hours at room temperature. Part of the solvent is then distilled off under reduced pressure and the crystalline residue is filtered to yield 53 g (= 79% of theory) of pure 5-chloro-2-(ω-ethylthioureido)-α-methyl-α-phenylbenzyl alcohol melting at 101°C to 103°C. On crystallization from benzene + petroleum ether a higher-melting modification melting at 112°C to 114°C is sometimes obtained.

(b) 33.5 g of the thiourea derivative obtained under (a) are mixed with 43 g of mercury oxide in 300 ml of ethanol and stirred and refluxed for 30 minutes. The reaction mixture is filtered hot and the solvent is evaporated, to yield 2-ethyl-amino-4-methyl-4-phenyl-6-chloro-4H-3,1-benzoxazine as an almost colorless oil which soon solidifies in crystalline form. Recrystallization from petroleum ether furnishes 26 g (= 87% of theory) of colorless crystals melting at 90°C to 92°C.

References

Merck Index 3814
DFU 6 (9) 550 (1981)
DOT 9 (6) 242 (1973)
Kuch, H., Schmitt, K., Seidl, G. and Hoffmann, I.; U.S. Patent 3,725,404; April 3, 1973; assigned to Farbwerke Hoechst AG

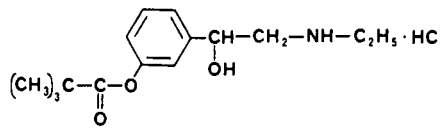
ETILEFRINE PIVALATE HYDROCHLORIDE

Therapeutic Function: Adrenergic

Chemical Name: 1-(3'-Pivaloyloxyphenyl)-2-ethylaminoethanol-1 hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 943-17-9; 709-55-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Circupon	Troponwerke	W. Germany	1972
Amphodyn	Klinge	W. Germany	–
Effortil	Boehr/Ingel	W. Germany	–
Ethyfron	Sawai	Japan	–
Eti-Puren	Klinge	W. Germany	–
Hishiherin-S	Hishiyama	Japan	–
Hyurina	Seiko	Japan	–
Presotona	Erco	Denmark	–
Pulsamin	Teikoku	Japan	–
Soledoton M	Soledum	W. Germany	–
Theoral	S.S. Pharm.	Japan	–
Tonus-Forte	Sanorania	W. Germany	–
Tri-Effortil	Boehr/Ingel.	W. Germany	–

Raw Materials

1-(3'-Hydroxyphenyl)-2-(N-benzylaminomethyl)ethan-1-one
Pivalic anhydride
Hydrogen

Manufacturing Process

30 parts of 1-(3'-hydroxyphenyl)-2-(N-benzylaminomethyl)-ethan-1-one are mixed with 100 parts of pyridine and 30 parts of pivalic anhydride and dissolved while warming. After heating for 1 hour under reflux, the acylation is complete. After concentrating the reaction solution, the product is precipitated from acetone/ether. Yield: 96.4% of 1-(3'-pivaloyloxyphenyl)2-(N-benzylaminomethyl)-ethan-1-one.

3 parts of palladium/charcoal (10% strength) are prehydrogenated in water, thereafter 10 parts of 1-(3'-pivaloyloxyphenyl)-2-(N-benzylaminoethyl)-ethan-1-one, dissolved in a 10-fold amount of water, are added dropwise at room temperature and hydrogenation is carried out until 1 mol of hydrogen has been taken up. After filtering off the catalyst, a further 3 parts of palladium/charcoal are added and hydrogenation is carried out until a further mol of hydrogen has been taken up. The catalyst is separated off and after removal of the solvent the hydrogenation product is reprecipitated from acetone/petroleum ether and from methanol/ether until it is pure according to thin layer chromatography. Yield: 38.8% of 1-(3'-pivaloyloxyphenyl)-2-ethylaminoethanol-1 hydroxide, melting point 208°C to 209°C.

References

Merck Index 3815
DFU 4 (6) 413 (1979)

Kleeman & Engel p. 378
I.N. p. 403
Chemisch-Pharmazeutische Fabrik, Adolf Klinge and Co.; British Patent 1,358,973; July 3, 1974

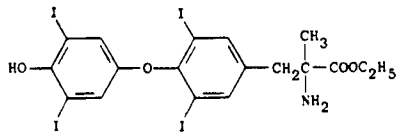
ETIROXATE

Therapeutic Function: Antihyperlipoproteinemic

Chemical Name: O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodo-α-methyl tyrosine ethyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 17365-01-4

Trade Name	Manufacturer	Country	Year Introduced
Skleronorm	Gruenenthal	W. Germany	1977

Raw Materials

α-Methylthyroxine
Ethanol

Manufacturing Process

7.91 g of α-methyl thyroxine are suspended in 150 cc of ethanol. While heating, the solution is saturated with dry hydrogen chloride. Thereafter, the solvent is distilled off at reduced pressure. The residue is dissolved in a mixture of ethanol and water (1:1). Adding a 5% solution of sodium hydrogen carbonate in water, the ethyl ester of α-methyl thyroxine precipitates; melting point: 156°C to 157°C after recrystallization from ethanol. The yield is 6.05 g, i.e., 74% of the theoretical yield.

References

Merck Index 3820
Kleeman & Engel p. 378
DOT 13 (5) 197 (1977)
I.N. p. 404
Kummer, H. and Beckmann, R.; U.S. Patent 3,930,017; December 30, 1975

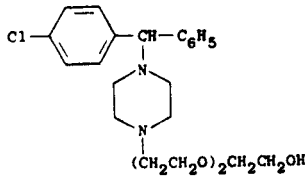
ETODROXIZINE

Therapeutic Function: Hypnotic

Chemical Name: 2-[2-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl] ethoxy] ethoxy] ethanol

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 17692-34-1

Trade Name	Manufacturer	Country	Year Introduced
Vesparax	UCB Chemie	W. Germany	1973
Drimyl	Cassenne	France	—
Indunox	UCB	—	—

Raw Materials

1-(2'-Hydroxyethyl)piperazine
p-Chlorobenzhydryl chloride
Diethylene glycol
Thionyl chloride
Potassium carbonate

Manufacturing Process

A mixture of 1.5 mols of 1-(2'-hydroxyethyl)piperazine and 1 mol of p-chlorobenzhydryl chloride is heated at 150°C for 15 minutes. The substance is dissolved in water, basified by caustic soda and extracted with benzene.

By purifying the benzene extract in vacuo, a 75% yield is obtained of 1-p-chlorobenzhydryl-4-(2'-hydroxyethyl)piperazine which has a boiling point of 205°C/0.02 mm Hg.

0.2 mol of 1-p-chlorobenzhydryl-4-(2'-hydroxyethyl)piperazine is dissolved in 300 cc of dry benzene and a solution of 36 grams of thionyl chloride in 100 cc of dry benzene is added cold with agitation. Reflux heating is then carried out until sulfur dioxide has ceased to be evolved.

The solvent is evaporated in vacuo, the residue is dissolved in anhydrous acetone and the hydrochloride formed is filtered. The corresponding base is liberated by treating the aqueous solution of this hydrochloride with an excess of potassium carbonate. A benzene extraction is effected and the benzene solution of the base is dried over potassium carbonate.

This benzene solution is then added to an equimolecular solution of the monosodium derivative of diethyleneglycol in a considerable excess of diethyleneglycol. The benzene is removed by distillation and the residue is heated in a boiling water-bath with agitation for 3 hours.

The excess diethyleneglycol is removed in vacuo and the residue dissolved in water and then in benzene. The benzene extract is washed several times in water, then purified in vacuo. The 1-p-chlorobenzhydryl-4-(2'-[2"-(2"'-hydroxyethoxy)-ethoxy]-ethyl)piperazine obtained distills at 250°C/0.01 mm Hg.

References

Merck Index 3823
Kleeman & Engel p. 379
I.N. p. 404
Morren, H.; British Patent 817,231; July 29, 1959

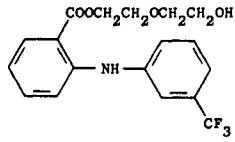
ETOFENAMATE

Therapeutic Function: Antiinflammatory

Chemical Name: 2-[[-3-(Trifluoromethyl)phenyl]amino]benzoic acid-2-(2-hydroxyethoxy)-ethyl ester

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 30544-47-9

Trade Name	Manufacturer	Country	Year Introduced
Rheumon	Troponwerke	W. Germany	1977
Rheumon	Bayer	Switz.	1979
Bayrogel	Bayro Pharm	Italy	1980
Flogoprofen	Wassermann	Spain	—

Raw Materials

N-(3-Trifluoromethylphenyl)anthranilic acid
2-(2-Chloroethoxy)ethanol

Manufacturing Process

16.0 g (0.05 mol) of the potassium salt of N-(3-trifluoromethylphenyl)-anthranilic acid are dissolved in 60 ml of dimethylformamide and heated to 110°C, and 6.2 g (0.05 mol) of 2-(2-chloroethoxy)-ethanol are slowly added. The reaction mixture is then heated to boiling for 2 hours. The precipitated potassium chloride is filtered off and the solvent is removed by evaporation. The residue is separated over a column with 400 g of silica gel (particle size 0.05 to 0.2 mm), using a 1:1 mixture of cyclohexane and glacial acetic acid as eluting agent. 16.0 g of the 2-(2-hydroxyethoxy)-ethyl ester of N-(3-trifluoromethylphenyl)-anthranilic acid are obtained in the form of a pale yellow oil which does not crystallize and cannot be distilled.

References

Merck Index 3824
Kleeman & Engel p. 380
DOT 14 (1) 9 (1978)
I.N. p. 404
Boltze, K.H., Brendler, O. and Lorenz, D.; U.S. Patent 3,692,818; September 19, 1972; assigned to Troponwerke Dinklage & Co. (W. Germany)

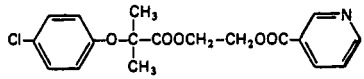
ETOFIBRATE

Therapeutic Function: Hypolipemic

Chemical Name: 2-Hydroxyethylnicotinate-2-(p-chlorophenoxy)-2-methyl propionate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 31637-97-5

Trade Name	Manufacturer	Country	Year Introduced
Lipo-Merz	Merz	W. Germany	1974
Noflevan	Alter	Spain	–

Raw Materials

2-(p-Chlorophenoxy)-2-methylpropionic acid
Ethylene oxide
Nicotinic acid

Manufacturing Process

A stream of ethylene oxide is passed through a solution of 107 g of 2-(p-chlorophenoxy)-2-methylpropionic acid and 2 g of zinc chloride in 200 ml of toluene, previously heated to between 55°C and 60°C, until 24 g of the gas have been dissolved. The reaction is allowed to continue for five hours, with gentle stirring. After this time has elapsed, the solution is cooled and washed successively with water, dilute ammonia and water until its pH becomes neutral. It is dried over anhydrous sodium sulfate, the solvent is separated off under vacuum, and the resulting liquid is the monoglycol ester of 2-(p-chlorophenoxy)-2-methylpropionic acid.

The product thus prepared is sufficiently pure to be used in the subsequent reaction. In this way, 107 g of the ester are prepared, which represents a yield of 83%.

To a solution of 93.8 g of the monoglycol ester in 500 ml of benzene, there are added 55 g of nicotinic acid chloride and 25 g of trimethylamine dissolved in 200 ml of benzene. The solution is stirred gently at a temperature of 60°C for two hours. After this time, the solution is cooled and washed successively with water, dilute hydrochloric acid, dilute ammonia and water until neutrality, it is dried over anhydrous sodium sulfate, and the solvent is evaporated under vacuum: in this way 110 g of glycol 2-(p-chlorophenoxy)-2-methylpropionate nicotinate is prepared, which represents a yield of 84%. The product is a slighly yellow oil having a refraction index of $n_D^{20} = 1.5422$ and which is distilled with decomposition at 214°C at a pressure of 0.3 mm.

References

Kleeman & Engel p. 380
DOT 11 (2) 459 (1975)
I.N. p. 405
Letelier, C.S. and Grafulla, F.C.; U.S. Patent 4,028,369; June 7, 1977; assigned to Alter S.A. (Spain)

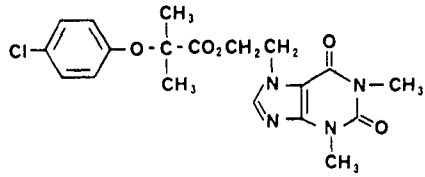
ETOFYLLINE CLOFIBRATE

Therapeutic Function: Hypolipemic

Chemical Name: 1-(Theophyllin-7-yl)ethyl 2-(p-chlorophenoxy)isobutyrate

Common Name: Theofibrate

Structural Formula:



Chemical Abstracts Registry No.: 519-37-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Duolip	Merckle	W. Germany	1981
Duolip	Mepha	Switz.	1981

Raw Materials

2-(p-Chlorophenoxy)isobutyric acid
7-Hydroxyethyltheophylline

Manufacturing Process

107.3 g (0.5 mol) 2-(p-chlorophenoxy) isobutyric acid and 56.0 g (0.25 mol) 7-hydroxyethyltheophylline were suspended together in 250 ml xylene. They were heated together for 15 hours in a water separator following the addition of 1.5 g p-toluenesulfonic acid. The solution was next agitated with dilute sodium bicarbonate solution (0.5 mol $NaHCO_3$), water washed and evaporated in a rotary evaporator.

The residue was then crystallized from isopropanol, yielding 58.0 g (55% yield) of 1-(7-theophyllinyl)-2-ethyl [2-(p-chlorophenoxy)-isobutyrate]. The compound had a melting point of 131°C to 132°C.

References

Merck Index 9113
DFU 2 (12) 800 (1977)
Kleeman & Engel p. 381
DOT 17 (9) 370 (1981)
I.N. p. 405
Metz, G. and Specker, M.; U.S. Patent 3,984,413; October 5, 1976; assigned to L. Merckle K.G. (W. Germany)

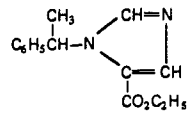
ETOMIDATE HYDROCHLORIDE

Therapeutic Function: Intravenous hypnotic

Chemical Name: 1-(1-Phenylethyl)-5-(ethoxy-carbonyl)imidazole hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 33125-97-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hypnomidate	Janssen	W. Germany	1977
Hypnomidate	Janssen	U.K.	1979
Amidate	Abbott	U.S.	1983
Radenarcon	Arzneimittelwerk Dresden	E. Germany	–

Raw Materials

dl-1-Phenylethylamine
Formic acid
Potassium thiocyanate
Sodium carbonate
Ethyl chloroacetate
Sodium
Nitric acid

Manufacturing Process

To a mixture of 1,115 parts dl-1-phenylethylamine and 950 parts dimethylformamide are added successively 655 parts triethylamine and 1,130 parts ethyl chloroacetate. After the addition is complete, the whole is stirred overnight. Then there are added 5,600 parts anhydrous ether and the whole is filtered.

The filtrate is washed four times with water, dried and evaporated, yielding dl-N-[(ethoxycarbonyl)methyl]-1-phenylethylamine. This residue is dissolved in 4,800 parts xylene while refluxing and to this solution are added 450 parts formic acid. After boiling for a few hours, the mixture is cooled and washed successively three times with a 20% solution of formic acid, water, sodium hydrogen carbonate solution.

The organic layer is then dried, filtered and evaporated. The oily residue is distilled in vacuo, yielding 1,600 parts dl-N-formyl-N-[(ethoxycarbonyl)methyl]-1-phenylethylamine (boiling point 160°C to 170°C at 0.8 mm pressure). 30 parts of a sodium dispersion, 50% in paraffin oil are added to 450 parts tetrahydrofuran and the whole is slowly heated to a temperature of 40°C, while stirring. While maintaining this temperature (cooling on a water bath is necessary) there are added portionwise 30 parts ethanol.

After the addition is complete, the whole is cooled on an ice bath and there is added dropwise a solution of 144 parts dl-N-formyl-N-[(ethoxycarbonyl)methyl]-1-phenylethylamine in 133 parts ethyl formate. After the addition is complete, the mixture is stirred overnight at room temperature.

Then there are added 160 parts ether. After stirring for 5 minutes the mixture is poured into 1,500 parts water. The aqueous layer is separated, washed twice with 80 parts diisopropyl ether and then there are added successively 114 parts concentrated hydrochloric acid and 90 parts potassium thiocyanate in 200 parts water. The mixture is stirred for 24 hours, whereupon an oil is separated.

After the addition of 750 parts water, a crystalline product is precipitated. The mixture is further stirred overnight. The solid is then filtered off and recrystallized from a mixture of ethanol and water (1:1 by volume) to yield dl-1-(1-phenylethyl)-2-mercapto-5-(ethoxycarbonyl)imidazole; its melting point is 129.8°C to 130.8°C.

To a stirred mixture of 140 parts nitric acid (d = 1.37), 1 part sodium nitrate and 240 parts water are added portionwise 89 parts dl-1-(1-phenylethyl)-2-mercapto-5-(ethoxycarbonyl)-imidazole. After the addition is complete, the whole is stirred for 2 hours at room temperature. The free base is liberated by addition of solid sodium carbonate and the whole is extracted with 120 parts anhydrous ether while heating. The aqueous layer is separated and extracted twice with 80 parts anhydrous ether.

The combined extracts are dried over magnesium sulfate, filtered and to the filtrate is added

2-propanol previously saturated with gaseous hydrogen chloride. The precipitated salt is filtered off, dried for 2 days at 60°C, to yield dl-1-(1-phenylethyl)-5-(ethoxycarbonyl)imidazole hydrochloride. It has a melting point 142°C to 142.8°C.

References

Merck Index 3828
DFU 1 (10) 461 (1976)
Kleeman & Engel p. 381
OCDS Vol. 3 p. 135 (1984)
DOT 15 (11) 475 (1979)
I.N. p. 405
REM p. 1044
Godefroi, E.F. and Van Der Eijcken, C.A.M.; U.S. Patent 3,354,173; November 21, 1967; assigned to Janssen Pharmaceutica NV (Belgium)

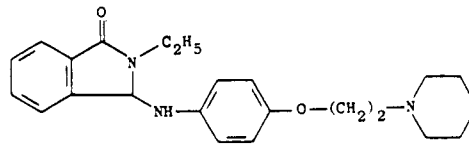
ETOMIDOLINE

Therapeutic Function: Muscle relaxant

Chemical Name: 2-Ethyl-2,3-dihydro-3-[[4-[2-(1-piperidinyl)ethoxy] phenyl] -amino] -1H-isoindol-1-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Smedolin	Yamanouchi	Japan	1976
Amidoline	Erba	Italy	–

Raw Materials

1-oxo-3-(Aminophenyl-p-ethoxypiperidino)isoindoline
Sodium hydride
Ethyl iodide

Manufacturing Process

31.3 g of 1-oxo-3-(aminophenyl-p-ethoxypiperidino)-isoindoline (0.0892 mol) are dissolved in 500 ml of anhydrous N,N-dimethylformamide. To this solution 5.75 g of NaH (0.105 mol) and 7.24 ml of CH_2CH_2I (0.0945 mol) are added and the resulted mixture is heated at 70°C for 1 hour, and then poured into an excess of water. 1-oxo-2-ethyl-3-(aminophenyl-p-ethoxy-piperidino)-isoindoline (MP 106°C to 107°C) is obtained by crystallization with ligroin.

1-oxo-2-ethyl-3-(iminophenyl-p-ethoxypiperidino)-isoindoline (MP 103°C to 104°C) is obtained as a byproduct with the above compound. This latter compound was reduced to produce 1-oxo-2-ethyl-3-(aminophenyl-p-ethoxypiperidino)-isoindoline.

References

Merck Index 3829
I.N. p. 406
Giraldi, P.N. and Mariotti, V.; U.S. Patent 3,624,206; November 30, 1971; assigned to Carlo Erba S.p.A. (Italy)

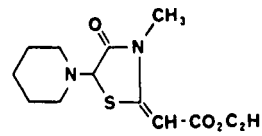
ETOZOLIN

Therapeutic Function: Diuretic

Chemical Name: 2-Carbethoxymethylene-3-methyl-5-piperidino-thiazolidin-4-one ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 73-09-6

Trade Name	Manufacturer	Country	Year Introduced
Elkapin	Goedecke	W. Germany	1977
Elkapin	Goedecke	Italy	1983
Etopinil	Wassermann	Spain	–

Raw Materials

2-Carbethoxymethylene-3-methyl-4-thiazolidinone
Bromine
Piperidine

Manufacturing Process

To a stirred solution of 20 g (0.1 mol) 2-carbethoxymethylene-3-methyl-4-thiazolidinone in 120 ml chloroform is added, dropwise, a solution of 5 ml (0.1 mol) bromine in 20 ml chloroform. The solvent is removed by distillation and the residue crystallized from methanol to yield 18 g (65%) of 2-carbethoxymethylene-3-methyl-5-bromo-4-thiazolidinone, MP 76°C.

To a solution of 28 g (0.1 mol) 2-carbethoxymethylene-3-methyl-5-bromo-4-thiazolidinone prepared as described in 200 ml benzene is added (0.2 mol) piperidine and the mixture is allowed to stand for 3 hours at 25°C. The resulting suspension is filtered to remove the precipitated piperidine hydrobromide and the filtrate is evaporated to dryness. The residue is taken up in ether, filtered and the filtrate saturated with dry hydrogen chloride to yield the hydrochloride salt of 2-carbethoxymethylene-3-methyl-5-piperidino-4-thiazolidinone, MP 158°C to 159°C.

References

Merck Index 3835
DFU 3 (4) 282 (1978)
Kleeman & Engel p. 383
DOT 14 (6) 239 (1978)

I.N. p. 407

Satzinger, G.; U.S. Patent 3,072,653; January 8, 1963; assigned to Warner-Lambert Pharmaceutical Co.

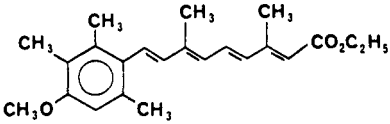
ETRETINATE

Therapeutic Function: Antipsoriasis (and antitumor)

Chemical Name: Ethyl all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Tigason	Roche	U.K.	1981
Tigason	Roche	Switz.	1982
Tigason	Roche	France	1983
Tigason	Roche	W. Germany	1983
Tigason	Roche	Sweden	1983
Tigason	Sauter	Switz.	–

Raw Materials

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-diene-1-triphenylphosphonium bromide
Sodium hydride
3-Formylcrotonic acid butyl ester
Potassium hydroxide
Ethyl iodide
Potassium carbonate

Manufacturing Process

228 g of 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide are introduced under nitrogen gassing into 910 ml of dimethylformamide and treated with cooling at 5°C to 10°C within 20 minutes with 17.5 g of a suspension of sodium hydride (about 50% by weight) in mineral oil. The mixture is stirred for 1 hour at about 10°C, then treated at 5°C to 8°C dropwise with 61.8 g of 3-formylcrotonic acid butyl ester, heating for 2 hours at 65°C, subsequently introduced into 8 liters of ice water, and, after the addition of 300 g of sodium chloride, thoroughly extracted with a total of 18 liters of hexane. The extract is washed 5 times with 1 liter of methanol/water (6:4 parts by volume) each time and 2 times with 1.5 liter of water each time, dried over sodium sulfate and evaporated under reduced pressure to leave 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester, MP 80°C to 81°C as the residue.

125.8 g of 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid

butyl ester are introduced into 2,000 ml of abs. ethanol and treated with a solution of 125.8 g of potassium hydroxide in 195 ml of water. The mixture is heated to boiling under nitrogen gassing for 30 minutes, then cooled, introduced into 10 liters of ice water and, after the addition of about 240 ml of concentrated hydrochloric acid (pH 2-4), thoroughly extracted with a total of 9 liters of methylene chloride. The extract is washed with about 6 liters of water to neutrality, dried over calcium chloride and evaporated under reduced pressure. The residue is taken up in 700 ml of hexane. The precipitated 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts at 228°C to 230°C.

60 g of 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid are dissolved in 1,000 ml of acetone. After the addition of 128 g of ethyl iodide and 128 g of potassium carbonate, the solution is stirred under nitrogen gassing for 16 hours at 55°C to 60°C and subsequently evaporated under reduced pressure. The residue is dissolved in 1,300 ml of petroleum ether (BP 80°C to 105°C). The 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester crystallizing out at -20°C, melts at 104°C to 105°C.

References

Merck Index 3836
DFU 2 (3) 199 (1977) (As Ro 10/9359) & 4 (12) 911 (1979) (As Etretinate)
DOT 18 (3) 120 (1982)
I.N. p. 407
Bollag, W., Ruegg, R. and Ryser, G.; U.S. Patent 4,105,681; August 8, 1978; assigned to Hoffmann-La Roche, Inc.
Bollag, W., Ruegg, R. and Ryser, G.; U.S. Patent 4,215,215; July 29, 1980; assigned to Hoffmann-La Roche, Inc.

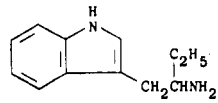
ETRYPTAMINE

Therapeutic Function: Central stimulant

Chemical Name: α-Ethyl-1H-indole-3-ethanamine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 2235-90-7

Trade Name	Manufacturer	Country	Year Introduced
Monase	Upjohn	U.S.	1961

Raw Materials

3-(2'-Ethyl-2'-nitrovinyl)indole
Hydrogen

Manufacturing Process

A mixture of 5 parts of 3-(2'-ethyl-2'-nitrovinyl)indole in 80 parts of ethanol saturated with ammonia gas is shaken in an atmosphere of hydrogen at 100 atmospheres pressure and at 20°C

in the presence of 1 part of a 5% palladium on carbon catalyst until the theoretical amount of hydrogen is absorbed. The catalyst is removed by filtration. The ethanol and ammonia are then removed from the filtrate by distillation under reduced pressure. The residual oil is dissolved in 170 parts of dry ether, 50 parts of potassium hydroxide pellets are added and the solution is kept at 18°C to 22°C for 2 hours. The mixture is filtered and hydrogen chloride is passed into the filtrate to precipitate crude α-ethyltryptamine hydrochloride. This is purified by crystallization from methanol/ethyl acetate and it then has a MP of 221°C.

References

Merck Index 3837
I.N. p. 407
Young, E.H.P.; British Patent 933,786; August 14, 1963; assigned to Imperial Chemical Industries Ltd.

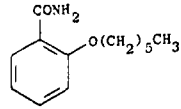
EXALAMIDE

Therapeutic Function: Antifungal

Chemical Name: 2-(Hexyloxy)benzamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53370-90-4

Trade Name	Manufacturer	Country	Year Introduced
Hyperan	S.S. Pharm	Japan	1980

Raw Materials

Salicylamide
Ethanol
Sodium
n-Hexyl bromide

Manufacturing Process

4.6 g sodium were dissolved in 150 ml ethanol and 27.4 g (0.2 mol) salicylamide added. The solution was refluxed gently and 24.6 g (0.2 mol) n-hexyl-bromide added gradually. The mixture was refluxed for six hours, the precipitated sodium bromide filtered off, and most of the alcohol removed by distillation. Water was then added to the residue, and the 2-n-hexyloxybenzamide filtered off. It crystallized from 50% aqueous ethanol in colorless crystals, MP 71°C.

References

Merck Index 3858
DOT 16 (8) 246 (1980)
I.N. p. 410
MacRae, F.J. and Seymour, D.E.; British Patent 726,786; June 5, 1952; assigned to Herts Pharmaceuticals Ltd.

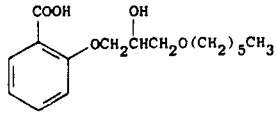
EXIPROBEN

Therapeutic Function: Choleretic

Chemical Name: 2-[3-(Hexyloxy)-2-hydroxypropoxy] benzoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 26281-69-6

Trade Name	Manufacturer	Country	Year Introduced
Droctil	Ciba Geigy	Italy	1971
Etopalin	Ciba Geigy	–	–

Raw Materials

p-Hydroxybenzoic acid methyl ester
3-Hexoxy-2-hydroxy-1-chloropropane
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

p-Hydroxy-benzoic acid methyl ester was subjected to a condensation reaction with 3-hexoxy-2-hydroxy-1-chloropropane in the presence of sodium ethylate and ethanol as a solvent, yielding p-(3-hexoxy-2-hydroxy)-propoxy-benzoic acid methyl ester.

62 g of this intermediate product were admixed with 250 cc of 2N sodium hydroxide and the resulting mixture was refluxed for three hours. The reaction mixture was allowed to cool and was made acid with concentrated hydrochloric acid while cooling it on ice. An oil separated out which was extracted with ether. The ether extract solution was dried over sodium sulfate and then the ether was distilled off, leaving a crystalline mass as a residue. The crystalline product was recrystallized from a mixture of benzene and petroleum ether, yielding a compound having a MP of 68°C.

References

Merck Index 3860
I.N. p. 410
Ohnacker, G.; U.S. Patent 3,198,827; August 3, 1965; assigned to Boehringer Ingelheim G.m.b.H. (Germany)