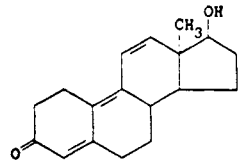
TRENBOLONE ACETATE

Therapeutic Function: Anabolic steroid

Chemical Name: 17β-Aceto-3-oxoestra-4,9,11-triene-3-one

Common Name: Trienolone acetate

Structural Formula:



(base)

Chemical Abstracts Registry No.: 10161-34-9; 10161-33-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Parabolan	Negma	France	1980
Finaject	Distrivet	France	–
Finaplix	Distrivet	France	–
Hexabolan	Phartec	France	–

Raw Materials

17β-Benzyloxy-4,5-seco-estra-9,11-diene-3,5-dione
Sodium-t-amylate
Acetic acid
Methanol
Acetic anhydride

Manufacturing Process

Stage A: Preparation of 17β-Benzoyloxy-Estra-4,9,11-Trien-3-one – 0.400 g of 17β-benzoyloxy-4,5-seco-estra-9,11-diene-3,5-dione is dissolved in 4 cc of toluene under an inert atmosphere. The solution is cooled to 3°C, then 0.48 cc is added of the solution of sodium tert-amylate in anhydrous toluene, diluted by the addition of a further 4.8 cc of anhydrous toluene.

This reaction mixture is kept between 0°C and +5°C for six hours, with agitation and under an inert atmosphere, then 5 cc of a 0.2 N solution of acetic acid in toluene are added. The mixture is extracted with toluene, and the extracts are washed with water and evaporated to dryness. The residue is taken up in ethyl acetate, and then the solution is evaporated to dryness in vacuo, yielding a resin which is dissolved in methylene chloride, and the solution passed through a column of 40 g of magnesium silicate. Elution is carried out first with methylene chloride, then with methylene chloride containing 0.5% of acetone, and 0.361 g is thus recovered of a crude product, which is dissolved in 1.5 cc of isopropyl ether; then hot methanol is added and the mixture left at 0°C for one night.

0.324 g of the desired 17β-benzoyloxy-estra-4,9,11-trien-3-one are thus finally obtained, being a yield of 85%, melting point is 154°C.

Stage B: Preparation of 17β-Hydroxy-Estra-4,9,11-Trien-3-one – 3 g of 17β-benzoyloxy-estra-4,9,11-trien-3-one, obtained as described in Stage A are dissolved in 15 cc of methanol. 0.03 g of hydroquinone is added, and the mixture is taken to reflux while bubbling in nitrogen. Then 1.2 cc of 11% methanolic caustic potash is added and reflux is maintained for three hours, after which the reaction product is acidified with 0.36 cc of acetic acid.

The methyl benzoate thus formed is eliminated by steam distillation, and 2.140 g of crude product are obtained, which are dissolved in 20 cc of methylene chloride. This solution is passed through 10 parts of magnesium silicate, elution being performed with 250 cc of methylene chloride containing 5% of acetone. After evaporation of the solvent 2.050 g of product is recovered, which is recrystallized from isopropyl ether.

In this way 1.930 g of the desired 17β-hydroxy-estra-4,9,11-trien-3-one is obtained being a yield of 89%, melting point is 186°C. It is converted to the acetate by acetic anhydride.

References

Merck Index 9402
Kleeman & Engel p. 908
DOT 12 (3) 121 (1976)
I.N. p. 968
Roussel-Uclaf; British Patent 1,035,683; July 13, 1966

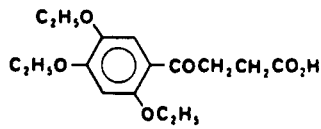
TREPIBUTONE

Therapeutic Function: Choleretic

Chemical Name: 3-(2',4',5'-Triethoxybenzoyl)-propionic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 41826-92-0

Trade Name	Manufacturer	Country	Year Introduced
Supacal	Takeda	Japan	1981
Cholibil	Takeda	Japan	–

Raw Materials

1,2,4-Triethoxybenzene
Succinic anhydride

Manufacturing Process

To a mixture of 7.5 parts by weight of 1,2,4-triethoxybenzene, 40 parts by volume of tetrachloroethane and 7.5 parts by weight of succinic anhydride are added 23 parts by weight of anhydrous aluminum chloride. The mixture is stirred for 1 hour at 25°C and for another 2 hours at 60°C. After addition of 50 parts by weight of ice and 50 parts by volume of concentrated hydrochloric acid, the reaction mixture is subjected to steam distillation.

After cooling crystals separated from the remaining liquid are collected by filtration and recrystallized from aqueous ethanol, whereby 2.5 parts by weight of 3-(2',4',5'-triethoxybenzoyl)-propionic acid are obtained as colorless needles, melting point 150°C to 151°C.

References

Merck Index 9404
DFU 3 (11) 846 (1978)
DOT 17 (12) 566 (1981)
I.N. p. 969
Mutara, T., Nohara, A., Sugihara, H. and Sanno, Y.; U.S. Patent 3,943,169; March 9, 1976; assigned to Takeda Chemical Industries, Ltd.

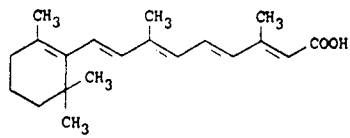
TRETINOIN

Therapeutic Function: Keratolytic

Chemical Name: 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

Common Name: Vitamin A acid; retinoic acid

Structural Formula:



Chemical Abstracts Registry No.: 302-79-4

Trade Name	Manufacturer	Country	Year Introduced
Aberel	McNeil	U.S.	1973
Vitamin-A-Saure	Roche	W. Germany	1973
Retin-A	Ortho	U.K.	1973
Airol	Roche	Italy	1975
Effederm	Sauba	France	1975
Retin-A	Cilag	Italy	1975
Acnelyse	Abdi Ibrahim	Turkey	—
Aknoten	Krka	Yugoslavia	—
Cordes-Vas	Icthyol-Ges.	W. Germany	—
Dermojuventus	Juventus	Spain	—
Epi-Aberel	Cilag	W. Germany	—
Eudyna	Nordmark	W. Germany	—
Stie Vaa	Stiefel	U.S.	—
Tretin-M	Ikapharm	Israel	—
Vitacid-A	Merima	Yugoslavia	—

Raw Materials

Beta-ionol
Triphenylphosphine hydrobromide
4-Methyl-1-al-hexadiene-(2,4)-acid-(6)

Manufacturing Process

100 parts of beta-ionol are dissolved in 200 parts of dimethylformamide and after the addition of 165 parts of triphenylphosphine hydrobromide, stirred for 7 hours at room temperature. Then 70 parts of 4-methyl-1-al-hexadiene-(2,4)-acid-(6) (melting point 177°C, white needles from water) are added to the now clear solution. 150 parts of isopropanol

are added and the whole cooled to -30°C. Into this solution, while stirring vigorously, 190 parts by volume of a 30% solution of sodium methylate in methanol are allowed to flow in. A vigorous exothermic reaction takes place and the temperature in the interior of the flask rises to +5°C. It is stirred for another 5 minutes and neutralized with 10% of sulfuric acid (until acid to Congo).

After stirring for 2 hours at room temperature, the mass of vitamin A acid has crystallized out. It is sharply filtered off by suction and washed with a little ice-cold isopropanol. From the filtrate, a further small amount of mainly all trans vitamin A acid crystallizes out upon the addition of water. The filter cake is suspended in 600 parts of water and stirred for 4 hours at room temperature; it is filtered by suction and the product washed with water. It is dried in vacuo at 40° to 50°C and 115 parts of vitamin A acid are obtained. The melting point lies between 146° and 159°C.

The mixture of the all trans and mainly 9,10-cis vitamin A acid may be separated by fractional crystallization from ethanol. All trans vitamin A acid has a melting point of 180° to 182°C and 9,10-cis vitamin A acid, which crystallized in the form of pale yellow fine needles collected into clusters, has a melting point of 189° to 190°C.

References

Merck Index 8065
Kleeman & Engel p. 910
PDR p. 1309
DOT 8 (8) 305 (1972)
I.N. p. 970
REM p. 785
Pommer, H. and Sarnecki, W.; U.S. Patent 3,006,939; October 31, 1961; assigned to Badische Anilin- & Soda-Fabrik AG, Germany

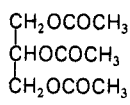
TRIACETIN

Therapeutic Function: Topical antifungal

Chemical Name: 1,2,3-propanetriol triacetate

Common Name: Glyceryl triacetate

Structural Formula:



Chemical Abstracts Registry No.: 102-76-1

Trade Name	Manufacturer	Country	Year Introduced
Enzactin	Ayerst	U.S.	1957
Fungacetin	Blair	U.S.	1957
Vanay	Ayerst	U.S.	1959

Raw Materials

Allyl acetate
Acetic acid
Oxygen

Manufacturing Process

200 grams of allyl acetate, 450 grams of glacial acetic acid and 3.71 grams of cobaltous bromide were charged to the reactor and the mixture was heated to 100°C. Pure oxygen was then introduced into the reactor below the surface of the liquid reaction mixture at the rate of 0.5 standard cubic feet per hour. Initially, all of the oxygen was consumed, but after a period of time oxygen introduced into the mixture passed through unchanged. During the course of the reaction, a small quantity of gaseous hydrogen bromide (a total of 1.9 grams) was introduced into the reaction zone, along with the oxygen. The reaction was allowed to continue for 6 hours following which the reaction mixture was distilled. Essentially complete conversion of the allyl acetate took place. A yield of 116 grams of glycerol triacetate was obtained, this being accomplished by distilling the glycerol triacetate overhead from the reaction mixture, at an absolute pressure of approximately 13 mm of mercury.

References

Merck Index 9407
PDR pp. 618, 1397
I.N. p. 970
REM p. 1231
Keith, W.C.; U.S. Patent 2,911,437; November 3, 1959; assigned to Sinclair Refining Co.

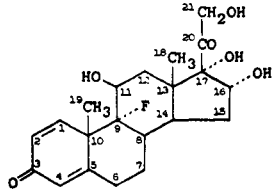
TRIAMCINOLONE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione

Common Name: Δ^1-16α-hydroxy-9α-fluorohydrocortisone

Structural Formula:



Chemical Abstracts Registry No.: 124-94-7

Trade Name	Manufacturer	Country	Year Introduced
Kenacort	Squibb	U.S.	1958
Aristocort	Lederle	U.S.	1958
Aristogel	Lederle	U.S.	1975
Albacort	Teknofarma	Italy	–
Cinolone	Pierrel	Italy	–
Cortinovus	Lampugnani	Italy	–
Delsolone	Medosan	Italy	–
Ditrizin	Ester	Spain	–
Eczil	Aesculapius	Italy	–
Flogicort	Francia	Italy	–

Trade Name	Manufacturer	Country	Year Introduced
Ipercortis	A.G.I.P.S.	Italy	–
Ledercort	Cyanamid	Italy	–
Medicort	Medici	Italy	–
Neo-Cort	Italchemi	Italy	–
Oticortrix	Oti	Italy	–
Sadocort	Guistini	Italy	–
Sedozalona	Loa	Argentina	–
Sterocort	Taro	Israel	–
Tedarol	Specia	France	–
Trialona	Alter	Spain	–
Triamcort	Helvepharm	Switz.	–
Triam-Oral	Nattermann	W. Germany	–
Tricortale	Bergamon	Italy	–
Trilon	Panther-Osfa	Italy	–
Volon	Heyden	W. Germany	–

Raw Materials

Bacterium *Corynebacterium simplex*
Δ^4-Pregnene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione-16,21-diacetate
Soy broth
Potassium hydroxide

Manufacturing Process

Preparation of $\Delta^{1,4}$-Pregnadiene-9α-Fluoro-11β,16α,17α,21-Tetrol 16,21-Diacetate: An agar slant of *Corynebacterium simplex* was washed with 5 ml of sterile saline and the spore suspension added to 100 ml of Trypticase soy broth in a 500 ml Erlenmeyer. The mixture was incubated at 32°C for 8 hr and 1 ml was used to inoculate 10 flasks, each containing 100 ml of Trypticase soy broth. The flasks were incubated with shaking at 32°C for 16 hr. 20 mg Δ^4-pregnene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione 16,21-diacetate dissolved in 2 ml ethanol was added and the flasks pooled. This solution was extracted several times with methylene chloride, washed with saturated saline and evaporated under reduced pressure. The residue was dissolved in methanol, treated with activated charcoal, filtered through diatomaceous earth and reevaporated to afford 277 mg of oil and acetylated overnight.

Paper strip chromatography showed approximately equal amounts of substrate and a more polar product ($\Delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione 16,21-diacetate) together with very small amounts of two less polar products. Partition chromatography of 0.25 gram of the residue (diatomaceous earth column; system: 2 parts ethyl acetate, 3 parts petroleum ether (90° to 100°C), 3 parts methanol and 2 parts water) separated the less polar products and the substrate. The desired most polar product remained on the column and was eluted with 500 ml of methanol. The residue (90 mg) from the evaporated methanol was repartitioned on diatomaceous earth [system: 3 parts ethyl acetate, 2 parts petroleum ether (90° to 100°C), 3 parts methanol, and 2 parts water] and the cut containing the desired product (determined by ultraviolet absorption spectrum) was evaporated under reduced pressure to afford 18 mg of solid.

Crystallization from acetone-petroleum ether gave 13 mg of colorless needles of $\Delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione 16,21-diacetate; melting point (Köfler block) about 150° to 240°C with apparent loss of solvent at 150°C. Recrystallization from acetone-petroleum ether did not alter the melting point.

Preparation of $\Delta^{1,4}$-Pregnadiene-9α-Fluoro-11β,16α,17α,21-Tetrol-3,20-Dione: A solution of 100 mg of $\Delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione 16,21-diacetate was dissolved in 10 ml of methanol and cooled to 0°C. After flushing with nitrogen, a solution of 35 mg of potassium hydroxide in 2 ml of methanol was added to the steroid solution. After standing at room temperature for 1 hour, the solution was neutralized

with glacial acetic acid and evaporated under a nitrogen atmosphere to a white solid. Water was added, and after cooling, the product was filtered and washed with water to afford 52 mg of $\Delta^{1,4}$-pregnadiene-9α-fluoro-11β,16α,17α,21-tetrol-3,20-dione, melting point 246° to 249°C. Three crystallizations from acetone-petroleum ether gave 29 mg of the tetrol, melting point 260° to 262.5°C, according to U.S. Patent 2,789,118.

References

Merck Index 9412
Kleeman & Engel p. 911
PDR pp. 830, 998, 1606
OCDS Vol. 1 p. 201 (1977) & 2, 185 (1980)
I.N. p. 971
REM p. 970
Bernstein, S., Lenhard, R.H. and Allen, W.S.; U.S. Patent 2,789,118; April 16, 1957; assigned to American Cyanamid Company
Allen, G.R., Marx, M. and Weiss, M.J.; U.S. Patent 3,021,347; February 13, 1962; assigned to American Cyanamid Company

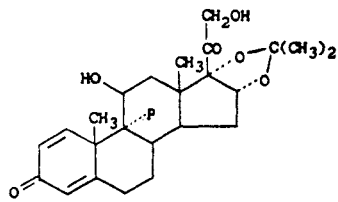
TRIAMCINOLONE ACETONIDE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-fluoro-11β,21-dihydroxy-16α,17[1-methylethylidenebis(oxy)] pregna-1,4-diene-3,20-dione

Common Name: 9α-fluoro-16α,17-isopropylidenedioxyprednisolone

Structural Formula:



Chemical Abstracts Registry No.: 76-25-5

Trade Name	Manufacturer	Country	Year Introduced
Kenalog	Squibb	U.S.	1958
Aristocort A	Lederle	U.S.	1958
Aristoderm	Lederle	U.S.	1960
Aristogel	Lederle	U.S.	1975
Triacort	Rowel	U.S.	1981
Trymex	Savage	U.S.	1982
Kenal	N.M.C.	U.S.	1982
Triaget	Lemmon	U.S.	1983
Acetospan	Reid Provident	U.S.	—
Adcortyl	Squibb	U.K.	—
Azmacort	Rorer	U.S.	—
Azobicina Triamcin	Maggioni	Italy	—
Cinonide	Legere	U.S.	—

Trade Name	Manufacturer	Country	Year Introduced
Cremocort	Rougier	Canada	–
Cutinolone	Labaz	France	–
Extracort	Basotherm	W. Germany	–
Flogicort	Francia	Italy	–
Ftorocort	Kobanyai	Hungary	–
Kenacort	Squibb	France	–
Kenacort-A	Squibb-Sankyo	Japan	–
Kortikoid	Ratiopharm	W. Germany	–
Ledercort N	Lederle	Japan	–
Lederspan	Lederle	U.K.	–
Mycolog	Squibb	U.S.	–
Myco-Triacet	Lemmon	U.S.	–
Mytrex	Savage	U.S.	–
Neo-Cort	Italchimici	Italy	–
Nyst-Olone	Schein	U.S.	–
Paralen	Heyden	W. Germany	–
Rineton	Sanwa	Japan	–
Sterocutan	Ifisa	Italy	–
Tedarol	Specia	Italy	–
Tramycin	Johnson & Johnson	U.S.	–
Triaderm	K-Line	Canada	–
Trialona	Alter	Spain	–
Triamalone	Trans-Canada Derm.	Canada	–
Triam-Injekt	Nattermann	W. Germany	–
Tricilone	Vangard	U.S.	–
Tricinolon	Kakenyaku	Japan	–
Volon	Heyden	W. Germany	–

Raw Materials

Triamcinolone
Acetone

Manufacturing Process

A solution of 250 mg of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione in 70 ml of hot acetone and 7 drops of concentrated hydrochloric acid is boiled for 3 minutes. After standing at room temperature for 17 hours, the reaction mixture is poured into dilute sodium bicarbonate and extracted with ethyl acetate. The extract is washed with saturated saline solution, dried and evaporated to a colorless glass. The residue is crystallized from acetone-petroleum ether to afford 166 mg of the acetonide, MP 270° to 274°C, decomposition, (with previous softening and browning). Three recrystallizations from acetone-petroleum ether give 113 mg of 9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione, MP 274° to 279°C, decomposition, (with previous softening and browning).

References

Merck Index 9413
Kleeman & Engel p. 912
PDR pp. 888, 999, 1003, 1033, 1429, 1535, 1604, 1746, 1750
OCDS Vol. 1 p. 201 (1977)
I.N. p. 971
REM p. 971
Bernstein, S. and Allen, G.R. Jr.; U.S. Patent 2,990,401; June 27, 1961; assigned to American Cyanamid Company
Hydorn, A.E.; U.S. Patent 3,035,050; May 15, 1962; assigned to Olin Mathieson Chemical Corporation

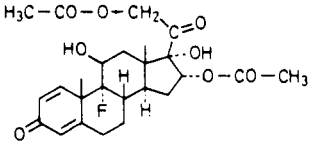
TRIAMCINOLONE DIACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione-17,21-diacetate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 67-78-7

Trade Name	Manufacturer	Country	Year Introduced
Aristocort	Lederle	U.S.	1959
Cenocort	Central	U.S.	1975
Cino-40	Tutag	U.S.	1976
Tracilon	Savage	U.S.	1978
Cinalone	Legere	U.S.	—
Delphicort	Lederle	W. Germany	—
Kenacort	Squibb	Italy	—
Ledercort	Lederle	Italy	—
Tedarol	Specia	France	—
Triam Forte	Hyrex	U.S.	—
Triamcin	Johnson & Johnson	U.S.	—

Raw Materials

16α,21-Diacetoxy-11β,17α-dihydroxy-9α-fluoro-4-pregnene-3,20-dione
Selenium dioxide

Manufacturing Process

To a solution of 16α,21-diacetoxy-11β,17α-dihydroxy-9α-fluoro-4-pregnene-3,20-dione (1.0 g) in tertiary-butanol (160 ml) and glacial acetic acid (1.6 ml) was added 600 mg of selenium dioxide, the mixture swept with nitrogen and kept at 70°C for 24 hours, selenium dioxide (350 mg) added, and the mixture swept with nitrogen and allowed to stand for another 24 hours. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The material so obtained was dissolved in ethyl acetate, washed with saturated sodium bicarbonate, water, cold freshly prepared ammonium sulfide solution, cold dilute ammonia water, cold dilute hydrochloric acid, and finally with water. After treatment with anhydrous sodium sulfate and activated charcoal, filtration through diatomaceous earth and evaporation to dryness under reduced pressure, 850 mg of a tan glass was obtained. Paper strip chromatographic analysis showed predominantly product plus a small amount of starting material. The 850 mg was chromatographed on 320 g of diatomaceous earth containing 160 ml of stationary phase of a solvent system composed of 3,4,3,2-ethyl acetate-petroleum ether (boiling point 90°C to 100°C), methanol, and water, respectively. The column dimensions were 3.8 cm x 78 cm with 460 ml hold back volume. The fifth and sixth hold back volumes were combined and evaporated under reduced pressure to 250 mg of product which, after a single crystallization from acetone-petroleum ether, gave 173 mg, melting point 150°C to 190°C. Paper strip chromatography showed a single spot having the same polarity as an authentic sample of 16α,21-diacetoxy-11β,17α-dihydroxy-9α-fluoro-1,4-pregnadiene-3,20-dione. A further crystallization from the same solvent pair gave 134 mg, melting point 185°C to 189°C, bubbles to 230°C.

References

Kleeman & Engel p. 913
PDR pp. 998, 1000, 1033
I.N. p. 971
REM p. 971
American Cyanamid Co.; British Patent 835,836; May 25, 1960

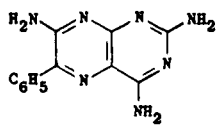
TRIAMTERENE

Therapeutic Function: Diuretic

Chemical Name: 6-phenyl-2,4,7-pteridinetriamine

Common Name: Ademine; pterophene

Structural Formula:



Chemical Abstracts Registry No.: 396-01-0

Trade Name	Manufacturer	Country	Year Introduced
Jatropur	Rohm	W. Germany	1962
Dytac	SKF	U.K.	1962
Teriam	Roussel	France	1963
Triamteril	Farmitalia	Italy	1963
Dyrenium	SKF	U.S.	1964
Diurene	Medix	Spain	–
Dyazide	SKF	U.S.	–
Kalistat	Disco	Israel	–
Maxzide	Lederle	U.S.	–
Triamthiazid	Henning	W. Germany	–
Urocaudal	Jorba	Spain	–

Raw Materials

5-Nitroso-2,4,6-triaminopyrimidine
Phenylacetonitrile

Manufacturing Process

To a solution of 9 grams of 5-nitroso-2,4,6-triaminopyrimidine in 500 ml of refluxing dimethylformamide is added 9 grams of phenylacetonitrile and the refluxing is stopped. The 3 grams of anhydrous sodium methoxide is added and the mixture is refluxed for 15 minutes. The mixture is chilled and the solid is filtered and washed several times with warm water until the washings are neutral. Drying gives yellow crystals which are recrystallized with a Darco treatment from formamide-water heating the solution no hotter than 125°C. This product is then suspended in filtered deionized water and warmed for 15 minutes. This yields the 2,4,7-triamino-6-phenylpteridine as yellow crystals with a MP of 314° to 317°C.

References

Merck Index 9415

Kleeman & Engel p. 915
PDR pp. 1014, 1713
OCDS Vol. 1 p. 427 (1977)
I.N. p. 972
REM p. 942
Weinstock, J. and Wiebelhaus, V.D.; U.S. Patent 3,081,230; March 12, 1963; assigned to Smith Kline & French Laboratories

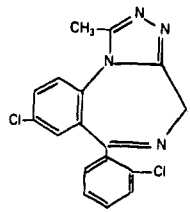
TRIAZOLAM

Therapeutic Function: Hypnotic

Chemical Name: 8-Chloro-1-methyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a] [1,4] -benzodiazepine

Common Name: Clorazolam

Structural Formula:



Chemical Abstracts Registry No.: 28911-01-5

Trade Name	Manufacturer	Country	Year Introduced
Halcion	Upjohn	Switz.	1978
Halcion	Upjohn	Italy	1978
Halcion	Upjohn	U.K.	1979
Halcion	Upjohn	W. Germany	1980
Halcion	Upjohn	U.S.	1982
Halcion	Sumitomo	Japan	1983
Halcion	Upjohn	Japan	1983
Songar	Valeas	Italy	1983
Novidorm	Sintyal	Argentina	–

Raw Materials

7-Chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepine-2-thione
Acetic acid hydrazide

Manufacturing Process

A mixture of 1.0 g (0.0031 mol) of 7-chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepine-2-thione, 0.8 g (0.0108 mol) of acetic acid hydrazide and 40 ml of 1-butanol was heated at reflux temperature under nitrogen for 24 hours. During the first 5 hours the nitrogen was slowly bubbled through the solution. After cooling and removing the solvent in vacuo, the product was well mixed with water and collected on a filter, giving 0.9 g of orange solid, melting point 210°C to 212°C. This was heated under nitrogen in an oil bath at 250°C and then cooled. The solid was crystallized from ethyl acetate, giving 0.5 g of tan solid of melting point 215°C to 216°C (decomposition). This was dissolved in 25 ml of 2-propanol,

filtered, concentrated to 10 ml and cooled, yielding 0.46 g (43%) of tan, crystalline 8-chloro-1-methyl-6-(o-chlorophenyl)-4H-s-triazolo[4,3-a] [1,4]-benzodiazepine of melting point 223°C to 225°C.

References

Merck Index 9418
DFU 1 (8) 393 (1976)
Kleeman & Engel p. 916
PDR p. 1843
OCDS Vol. 1 p. 368 (1977)
DOT 11 (5) 20 (1975) & 15 (1) 30 (1979)
I.N. p. 972
REM p. 1064
Hester, J.B. Jr.; U.S. Patents 3,741,957; June 26, 1973; 3,980,790; September 14, 1976; and 3,987,052; October 19, 1976; all assigned to The Upjohn Company

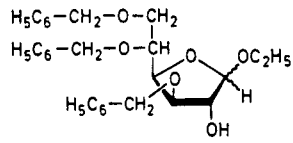
TRIBENOSIDE

Therapeutic Function: Treatment of venous disorders

Chemical Name: Ethyl-3,5,6-tris-O-(phenylmethyl)-D-glucofuranoside

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 10310-32-4

Trade Name	Manufacturer	Country	Year Introduced
Glyvenol	Ciba	W. Germany	1967
Glyvenol	Ciba Geigy	France	1968
Glyvenol	Ciba	Italy	1968
Hemocuron	Takeda	Japan	1978
Alven	Firma	Italy	–
Flebosan	Dukron	Italy	–
Venalisin	A.G.I.P.S.	Italy	–
Venex	Oti	Italy	–
Venodin	Tosi-Novara	Italy	–

Raw Materials

1,2-Isopropylidene glucofuranose
Benzyl chloride

Manufacturing Process

4.9 g of 3,5,6-tribenzyl-1,2-isopropylidene glucofuranose are kept overnight at room temperature with 100 cc of N-ethanolic hydrochloric acid. Evaporation under vacuum at below 50°C is then carried out and the residue taken up in 150 cc of chloroform. The chloroform solu-

tion is thoroughly washed with sodium bicarbonate solution, dried with calcined sodium sulfate and evaporated under vacuum. The oily residue is then distilled under vacuum with a free flame. In this manner there is obtained the ethyl-3,5,6-tribenzyl-D-glucofuranoside of boiling point 270°C to 275°C under 1 mm pressure.

The glucofuranose used as starting material is obtained as follows: 8.8 g of 1,2-isopropylidene-D-glucofuranose and 50.6 g of benzyl chloride are treated with a total of 28 g of potassium hydroxide in portions with cooling and stirring. The mixture is then stirred for 3 hours at 80°C to 90°C. Working up from chloroform solution and distillation at 250°C to 260°C under 0.1 mm pressure give 8.9 g of 1,2-isopropylidene-3,5,6-tribenzyl-D-glucofuranose.

References

Merck Index 9420
Kleeman & Engel p. 917
I.N. p. 973
Druey, J. and Huber, G.L.; U.S. Patent 3,157,634; November 17, 1964; assigned to Ciba Corp.

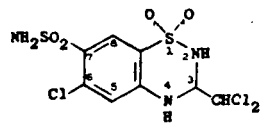
TRICHLORMETHIAZIDE

Therapeutic Function: Diuretic

Chemical Name: 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: Hydrotrichlorothiazide

Structural Formula:



Chemical Abstracts Registry No.: 133-67-5

Trade Name	Manufacturer	Country	Year Introduced
Naqua	Schering	U.S.	1960
Metahydrin	Merrell National	U.S.	1960
Esmarin	Merck	W. Germany	1960
Fluitran	Essex	Italy	1962
Trichlorex	Lannett	U.S.	1980
Achletin	Toyama	Japan	—
Aitruran	Horita	Japan	—
Anatran	Tobishi	Japan	—
Anistadin	Maruko	Japan	—
Aponorin	Kodama	Japan	—
Carvacron	Taiyo	Japan	—
Chlopolidine	Tsuruhara	Japan	—
Cretonin	Hokuriku	Japan	—
Diu-Hydrin	Darby	U.S.	—
Diurese	Amer. Urologicals	U.S.	—
Flutoria	Towa	Japan	—
Hidroalogen	Bicsa	Spain	—
Intromene	Teikoku	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Naquival	Schering	U.S.	–
Nydor	Taro	Israel	–
Pluvex	Firma	Italy	–
Polynease	Sawai	Japan	–
Sanamiron	Zensei	Japan	–
Schebitran	Nichiiko	Japan	–
Tachionin	San-A	Japan	–
Tolcasone	Toho	Japan	–
Trametol	Green Cross	Japan	–
Triazide	Legere	U.S.	–
Trichlordiuride	Formenti	Italy	–
Tricloretic	Irfi	Italy	–
Triflumen	Serono	Italy	–

Raw Materials

5-Chloro-2,4-disulfamylaniline
Dichloroacetaldehyde

Manufacturing Process

A mixture of 5.7 grams (0.02 mol) of 5-chloro-2,4-disulfamylaniline and 4.9 grams (0.04 mol) of dichloroacetaldehyde in 25 ml of dimethyl formamide was heated at the boiling temperature and under reflux for 30 minutes. The reaction mixture was thereafter poured into a mixture of ice and water to precipitate the desired 6-chloro-7-sulfamyl-3-dichloromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide as a crystalline solid melting at 250° to 270°C with decomposition.

References

Merck Index 9437
Kleeman & Engel p. 917
PDR pp. 1033, 1230, 1605, 1634
OCDS Vol. 1 p. 359 (1977)
I.N. p. 974
REM p. 941
Close, W.J.; U.S. Patent 3,264,292; August 2, 1966; assigned to Abbott Laboratories

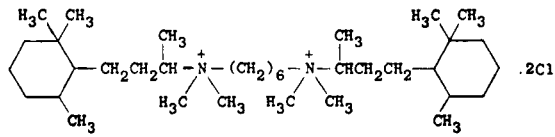
TRICLOBISONIUM CHLORIDE

Therapeutic Function: Topical antiseptic (vaginal)

Chemical Name: N,N,N',N'-tetramethyl-N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)-propyl]-1,6-hexanediaminium dichloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 79-90-3

Trade Name	Manufacturer	Country	Year Introduced
Triburon	Roche	U.S.	1959

Raw Materials

cis-Tetrahydroionone
Hydrogen
Formaldehyde
1,6-Hexanediamine
Formic acid
Methyl chloride

Manufacturing Process

To a solution of 49 grams (0.25 mol) of cis-tetrahydroionone and 14.1 grams (0.12 mol) of 1,6-hexanediamine in 150 ml of ethanol was added 1 teaspoon of Raney nickel. The volume was adjusted to 300 ml with ethanol and the mixture was hydrogenated at 50°C and a pressure of 200 psi. The catalyst was filtered off, the filtrate was concentrated and the residual oil fractionated in vacuo to obtain N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,6-hexanediamine; BP 192° to 202°C at 0.02 mm.

To 217 grams (0.456 mol) of N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,6-hexanediamine were added 182 ml (3.04 mols) of formic acid (90%). The resulting colorless solution was cooled, then 91.3 ml (1.043 mols) of formaldehyde (37%) were added. The solution was heated at steam temperature with occasional shaking for 2 hours and then refluxed for 8 hours. The volatiles were distilled off at steam temperature under water vacuum and the residual oil was made strongly alkaline with 50% potassium hydroxide. The reaction product was extracted with ether. The ether extract was washed with water, dried and concentrated in vacuo. The residual oil was fractionated in vacuo to obtain N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine, $BP_{0.4}$ 230° to 240°C, n_D^{26} = 1.4833. An aliquot, when treated with an ethanolic hydrogen chloride, gave the crystalline dihydrochloride, MP 183° to 185°C (recrystallized from ethanolacetonitrile).

To 5 grams of N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine dissolved in 100 ml of methanol, at 4°C, were added 100 ml methanol containing 10 grams of methyl chloride. The solution was heated in a closed vessel at 60°C for 15 hours. The colorless solution was concentrated and the resulting white solid crystallized from ethanol-acetonitrile-ether to obtain N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine bis(methochloride) hemihydrate.

References

Merck Index 9465
I.N. p. 975
Goldberg, M.W. and Teitel, S.; U.S. Patent 3,064,052; November 13, 1962; assigned to Hoffmann-La Roche Inc.

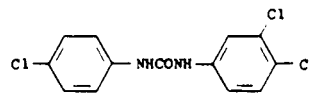
TRICLOCARBAN

Therapeutic Function: Disinfectant

Chemical Name: N-(4-Chlorophenyl)-N'-(3,4-dichlorophenyl)urea

Common Name: Trichlorocarbanilid

Structural Formula:



Chemical Abstracts Registry No.: 101-20-2

Trade Name	Manufacturer	Country	Year Introduced
Cutisan	Innothera	France	1960
Procutene	Bouty	Italy	1968
Nobacter	Innothera	France	–
Septivon-Lavril	Clin Midy	France	–
Solubacter	Innothera	France	–
Trilocarban	Armour-Montagu	France	–

Raw Materials

3,4-Dichloroaniline
4-Chlorophenyl isocyanate

Manufacturing Process

To a suitable reaction vessel equipped with a thermometer, agitator and reflux condenser and containing 8.1 parts by weight (substantially 0.05 mol) of 3,4-dichloroaniline in approximately 57 parts by weight of diethyl ether is added dropwise a solution of 7.7 parts by weight (substantially 0.05 mol) of 4-chlorophenyl isocyanate in approximately 15 parts by weight of diethyl ether at such a rate so as to maintain gentle reflux. Upon completion of the isocyanate addition the reaction mass is agitated for about one hour. The mass is filtered and the residue washed with diethyl ether. The dried product is a white fluffy solid which on recrystallization from ethanol gives fine white plates of 4,3',4'-trichlorocarbanilide, melting point 255.2°C to 256.0°C (88.0% yield).

References

Merck Index 9466
Kleeman & Engel p. 918
I.N. p. 975
Beaver, D.J. and Stoffel, P.J.; U.S. Patent 2,818,390; December 31, 1957; assigned to Monsanto Chemical Co.

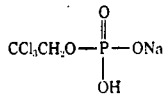
TRICLOFOS SODIUM

Therapeutic Function: Sedative, hypnotic

Chemical Name: 2,2,2-trichloroethanol dihydrogen phosphate monosodium salt

Common Name: Trichloroethyl phosphate monosodium salt

Structural Formula:



Chemical Abstracts Registry No.: 7246-20-6; 306-52-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Triclos	Merrell National	U.S.	1972
Tricloran	C.T.S.	Israel	–
Tricloryl	Glaxo	U.K.	–

Raw Materials

Trichloroethanol
Phosphorus oxychloride
Sodium carbonate

Manufacturing Process

Trichloroethanol (500 grams) and phosphorus oxychloride (510 grams) were added to dry diethyl ether (3.5 liters) and stirred at 10°C with ice/water cooling. Dry pyridine (270 ml) was added dropwise over 1 hour, maintaining the temperature below 25°C. The resulting suspension was stirred for a further 1 hour and then stood at 0°C overnight. The pyridine hydrochloride was removed by filtration and washed with diethyl ether (2 x 300 ml) and dried in vacuo over P_2O_5 to give 380 grams.

The ether filtrate and washings were evaporated at room temperature under reduced pressure to give a clear liquid residue (801 grams). This residue was distilled under high vacuum to give trichloroethyl phosphorodichloridate (556 grams, 62.4% of theory), boiling point 75°C/0.8 mm.

The phosphorodichloridate was hydrolyzed by adding to a stirred solution of sodium carbonate (253 grams) in water (2.9 liters). After 1 hour the solution was cooled and acidified with a solution of concentrated sulfuric acid (30 ml) in water (150 ml) and then extracted with a mixture of tetrahydrofuran and chloroform (2.3/1; 3 x 1 liter). The tetrahydrofuran/chloroform liquors were bulked and evaporated to dryness to give a light brown oil. This was dissolved in water (1 liter) and titrated with 2 N sodium hydroxide solution to a pH of 4.05 (volume required 930 ml). The aqueous solution was clarified by filtration through kieselguhr and then evaporated under reduced pressure to a syrup (737 grams).

Hot acetone (4.5 liters) was added to this syrup and the clear solution stood at room temperature for 2 hours and then at 0°C overnight. The white crystalline solid was filtered off, washed with acetone (2 x 400 ml) and dried at 60°C in vacuo to give sodium trichloroethyl hydrogen phosphate (414 grams, 49.3% of theory from trichloroethanol).

References

Merck Index 9469
Kleeman & Engel p. 918
I.N. p. 975
Hems, B.A., Arkley, V., Gregory, G.I., Webb, G.B., Elks, J. and Tomich, E.G.; U.S. Patent 3,236,920; February 22, 1966; assigned to Glaxo Laboratories Limited, England

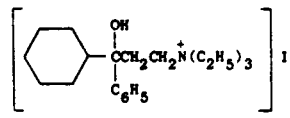
TRIDIHEXETHYL IODIDE

Therapeutic Function: Anticholinergic

Chemical Name: γ-Cyclohexyl-N,N,N-triethyl-γ-hydroxybenzene-propanaminium iodide

Common Name: Propethonium iodide; tridihexethide

Structural Formula:



Chemical Abstracts Registry No.: 125-99-5

Trade Name	Manufacturer	Country	Year Introduced
Pathilon	Burroughs Wellcome	U.S.	1955
Duosetil	Dessy	Italy	–

Raw Materials

Acetophenone
Diethylamine
Cyclohexyl bromide
Paraformaldehyde
Magnesium
Ethyl iodide

Manufacturing Process

Acetophenone, paraformaldehyde and diethylamine are first reacted to give ω-diethylamino-propiophenone. That is reacted with cyclohexylmagnesium bromide to give 3-diethylamino-1-cyclohexyl-1-phenylpropanol-1.

To 1,320 parts of methyl isobutyl ketone is added 570 parts of 3-diethylamino-1-cyclohexyl-1-phenylpropanol-1 (2 mols) and the mixture is stirred until solution is complete. Then 500 parts (3.2 mols or 60% excess) of ethyl iodide are added. After filtration, the filtrate is diluted with an additional 300 parts of methyl isobutyl ketone and the solution is then heated at the reflux temperature (108°C to 110°C) for 9 hours. After cooling to 0°C, the precipitated solid material is removed by filtration, washed with isopropyl acetate and dried. Approximately 777 parts of product is obtained or a yield of 88.6% based on as-is starting material or 92.5% based on real starting material.

References

Merck Index 9474
Kleeman & Engel p. 918
I.N. p. 976
REM p. 919
Lobby, J.; U.S. Patent 2,913,494; November 17, 1959; assigned to American Cyanamid Co.

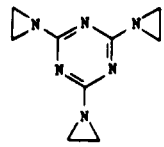
TRIETHYLENEMELAMINE

Therapeutic Function: Antineoplastic

Chemical Name: 2,4,6-Tris(1-aziridinyl)-s-triazine

Common Name: Tretamine

Structural Formula:



Chemical Abstracts Registry No.: 51-18-3

Trade Name	Manufacturer	Country	Year Introduced
Triethylene	Lederle	U.S.	1954
Triameline	I.C.I.	–	–

Raw Materials

Cyanuric chloride
Ethylene imine

Manufacturing Process

Cyanuric chloride (which may or may not contain the usual commercial impurities) is dispersed into ice water by stirring in a ratio of 18.8 g of cyanuric chloride to a mixture of 100 g of ice and 100 g of water. The slurry may conveniently be prepared directly in a 3-necked flask equipped with an agitator, dropping funnel, and thermometer. The temperature of the flask and contents is maintained within the range of 2°C to 5°C, with an ice-salt mixture. A solution of ethylenimine in an aqueous solution of potassium carbonate prepared in the proportions of 14 g ethylenimine, 44.5 g potassium carbonate, and 150 g of water, is added dropwise to the cyanuric chloride slurry. The reaction solution is then clarified with a little activated charcoal, filtered, and extracted with chloroform. Despite the fact that triethylenemelamine is more soluble in water than in chloroform, in a two-phase system (water-chloroform) nearly 75% of the triethylenemelamine is distributed in the chloroform, and hence a few extractions with that solvent suffice to separate the material from the original reaction medium. Five extractions with 50 ml portions of chloroform gave 19 g of product, and an additional 3 extractions with 25 ml portions gave 0.5 g, a total yield of 95.7%. The product obtained by evaporating such an extract is a white microcrystalline powder.

References

Merck Index 9481
I.N. p. 970
Wystrach, V.P. and Kaiser, D.W.; U.S. Patent 2,520,619; August 29, 1950; assigned to American Cyanamid Co.

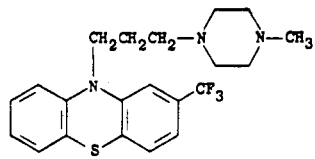
TRIFLUOPERAZINE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[3-(4-methylpiperazin-1-yl)propyl] -2-trifluoromethylphenothiazine

Common Name: Triftazin; triphthasine

Structural Formula:



Chemical Abstracts Registry No.: 117-89-5; 440-17-5 (Dihydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Stelazine	SKF	U.S.	1958
Terfluzine	Theraplix	France	1962
Triazine	Cord	U.S.	1981
Calmazine	Protea	Australia	—
Chemflurazine	Chemo-Drug	Canada	—
Dymoperazine	Dymond	Canada	—
Flurazine	Taro	Israel	—

Trade Name	Manufacturer	Country	Year Introduced
Jatroneural	Rohm	W. Germany	–
Modalina	Maggioni	Italy	–
Normaln P	Sawai	Japan	–
Novoflurazine	Novopharm	Canada	–
Pentazine	Pentagone	Canada	–
Sedizine	Trima	Israel	–
Solazine	Horner	Canada	–
Telazin	Dincel	Turkey	–
Terflurazine	Lennon	S. Africa	–
Tranquis	Sumitomo	Japan	–
Trifluoper-Ez-Ets	Barlow Cote	Canada	–
Triflurin	Paul Maney	Canada	–

Raw Materials

2-Trifluoromethylphenothiazine
Sodium amide
1-(3'-Chloropropyl)-4-methylpiperazine

Manufacturing Process

A mixture of 17.2 grams of 2-trifluoromethylphenothiazine, 3.1 grams of sodamide and 14 grams of 1-(3'-chloropropyl)-4-methylpiperazine in 200 ml of xylene is heated at reflux for 2 hours. The salts are extracted into 150 ml of water. The xylene layer is then extracted with several portions of dilute hydrochloric acid. The acid extracts are combined and neutralized with ammonium hydroxide solution. The product, '10-[3'-(4"-methyl-1"-piperazinyl)-propyl]-2-trifluoromethylphenothiazine, is taken into benzene and purified by vacuum distillation, BP 202° to 210°C at 0.6 mm.

References

Merck Index 9489
Kleeman & Engel p. 919
PDR pp. 1606, 1723, 1999
DOT 9 (6) 228 (1973)
I.N. p. 976
REM p. 1091
Ullyot, G.E.; U.S. Patent 2,921,069; January 12, 1960; assigned to Smith Kline & French Laboratories

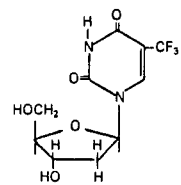
α,α,α-TRIFLUOROTHYMIDINE

Therapeutic Function: Antiviral (ophthalmic)

Chemical Name: 2'-Deoxy-5-(trifluoromethyl)uridine

Common Name: Trifluridine

Structural Formula:



Chemical Abstracts Registry No.: 70-00-8

Trade Name	Manufacturer	Country	Year Introduced
Trifluorothymidine	Mann	W. Germany	1975
Bephen	Thilo	W. Germany	–
Triherpine	Dispersa	Switz.	–
Viroptic	Burroughs-Wellcome	U.S.	–

Raw Materials

3',5'-Bis-O-(p-nitrobenzoyl)-2'-deoxy-5-(trifluoromethyl)uridine
Diisopropylamine

Manufacturing Process

A suspension of 4.00 g (6.75 mmol) of 3',5'-bis-O-(p-nitrobenzoyl)-2'-deoxy-5-(trifluoromethyl)uridine in 250 ml of methanol was treated with 10 ml of diisopropylamine and refluxed until it had dissolved (about 18 minutes), and the solution was concentrated. The dry residue was partitioned between 50 ml of chloroform and 50 ml of water. The chloroform layer was washed with 20 ml of water, and the combined aqueous layers were concentrated. A low ultraviolet extinction (ϵ7200 and 262 mμ; pH 1) and the presence of isopropyl signals in the NMR spectrum (two singlets at γ8.73 and 8.85) indicated the dry residue contained diisopropylamine, probably as a salt with the relatively acidic heterocyclic N–H in **14**.

A solution in 75 ml of water was treated with 8 ml (volume of resin) of Dowex 50 (H), prewashed with water and methanol. The resin was removed on a filter and washed with 25 ml of methanol and 50 ml of water. The combined filtrate was evaporated in vacuo to form 1.99 g of 2'-deoxy-4-(trifluoromethyl)uridine (100%), melting point 171°C to 175°C.

References

DFU 5 (11) 561 (1980)
Kleeman & Engel p. 921
PDR p. 768
DOT 16 (12) 430 (1980)
I.N. p. 977
REM p. 1232
Heidelberger, C.; U.S. Patent 3,201,387; August 17, 1965; assigned to the U.S. Secretary of Health, Education and Welfare
Ryan, K.J., Acton, E.M. and Goodman, L.; U.S. Patent 3,531,464; September 29, 1970; assigned to the U.S. Secretary of Health, Education and Welfare

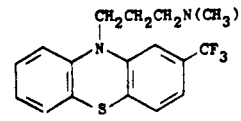
TRIFLUPROMAZINE

Therapeutic Function: Tranquilizer

Chemical Name: N,N-Dimethyl-2-(trifluoromethyl)-10H-phenothiazine-10-propanamine

Common Name: Fluopromazine

Structural Formula:



Chemical Abstracts Registry No.: 146-54-3; 1098-60-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Vesprin	Squibb	U.S.	1957
Psyquil	Squibb	France	1970
Fluomazina	Firma	Italy	–
Fluorofen	Savio	Italy	–
Nivoman	Heyden	W. Germany	–
Siquil	Iquinosa	Spain	–

Raw Materials

2-Trifluoromethylphenothiazine
Sodium amide
3-Chloro-1-dimethylaminopropane

Manufacturing Process

Approximately 3.8 grams of sodamide is freshly prepared from 2.25 grams of sodium, 90 grams of liquid ammonia and a catalytic trace of ferric nitrate. The ammonia is allowed to evaporate. A solution of 19.1 grams of 2-trifluoromethylphenothiazine (prepared by the Bernthsen thionation of 3-trifluoromethyldiphenylamine) in 160 ml of dry benzene is added to the reaction flask followed by 18 grams of 3-chloro-1-dimethylaminopropane. The reaction mixture is heated at reflux for 20 hours. After washing the cooled mixture with 130 ml of water, the organic layer is extracted with several portions of dilute hydrochloric acid. The acid extracts are combined and neutralized with ammonium hydroxide solution. The oily free base is extracted into benzene and purified by distillation to give 19.6 grams of 10-(3'-dimethylaminopropyl)-2-trifluoromethylphenothiazine, boiling point 177° to 181°C at 1 mm. The free base (7 grams) is converted to the hydrochloride salt by reacting an alcoholic solution of the base with hydrogen chloride gas. Evaporation of the volatiles in vacuo leaves an amorphous solid which is recrystallized from ethanol/ether to pink crystals, MP 173° to 174°C, the hydrochloride salt of the free base prepared above.

References

Merck Index 9492
Kleeman & Engel p. 920
OCDS Vol. 1 p. 380 (1977)
I.N. p. 977
REM p. 1092
Ullyot, G.E.; U.S. Patent 2,921,069; January 12, 1960; assigned to Smith Kline & French Laboratories

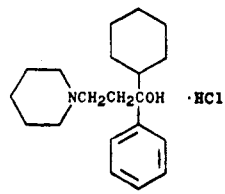
TRIHEXYPHENIDYL HYDROCHLORIDE

Therapeutic Function: Antiparkinsonian

Chemical Name: α-cyclohexyl-α-phenyl-1-piperidinepropanol hydrochloride

Common Name: Benzhexol chloride

Structural Formula:



Chemical Abstracts Registry No.: 52-49-3; 144-11-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Artane	Lederle	U.S.	1949
Pipanol	Winthrop	U.S.	1952
Tremin	Schering	U.S.	1964
Antitrem	Roerig	U.S.	1974
Anti-Spas	Protea	Australia	–
Aparkan	Chinoin	Hungary	–
Aparkane	I.C.N.	Canada	–
Broflex	Bio-Medical	U.K.	–
Novohexidyl	Novopharm	Canada	–
Paralest	Pharmachemie	Neth.	–
Pargitan	Kabi Vitrum	Sweden	–
Parkinane	Lederle	France	–
Parkopan	Fahlberg-List	E. Germany	–
Partane	Taro	Israel	–
Peragit	Gea	Denmark	–
Pyramistin	Yamanouchi	Japan	–
Rodenal	Abic	Israel	–
Sedrena	Daiichi	Japan	–
Trihexane	Darby	U.S.	–
Trihexy	Barlow Cote	Canada	–
Triphedinon	Toho	Japan	–

Raw Materials

Acetophenone
Piperidine
Magnesium
Paraformaldehyde
Cyclohexyl bromide
Hydrogen chloride

Manufacturing Process

Acetophenone, paraformaldehyde and piperidine are first reacted to give ω-(1-piperidyl)propiophenone.

To an absolute ethyl ether solution of cyclohexylmagnesium bromide (prepared from 261 parts of cyclohexyl bromide, 38.8 parts magnesium turnings and 700 parts by volume absolute ethyl ether) a dry solution of 174 parts omega-(1-piperidyl)-propiophenone in 600 parts by volume of ether is added, with stirring, at such a rate that gentle reflux is maintained with no external cooling or heating. The reaction mixture is stirred for about 5 hours and then allowed to stand at room temperature until reaction appears complete. While being cooled the reaction mixture is then decomposed by the dropwise addition of 500 parts by volume of 2.5 N hydrochloric acid, and finally is made strongly acidic to Congo red by the addition of concentrated hydrochloric acid.

The resulting white solid is collected on a filter, air dried, redissolved in 2,500 parts water at 95°C and the resulting solution treated with decolorizing charcoal and clarified by filtration. The cooled filtrate is made alkaline with ammonia and the product, crude 3-(1-piperidyl)-1-cyclohexyl-1-phenyl-1-propanol is collected. The hydrochloride melts with decomposition in ten seconds in a bath held at 258.5°C. The alcohol melts at 114.3° to 115.0°C, according to U.S. Patent 2,716,121.

References

Merck Index 9501
Kleeman & Engel p. 921
PDR p. 830
OCDS Vol. 1 p. 47 (1977)
DOT 9 (6) 247 (1973)

I.N. p. 978
REM p. 931
Adamson, D.W. and Wilkinson, S.; U.S. Patent 2,682,543; June 29, 1954; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Denton, J.J.; U.S. Patent 2,716,121; August 23, 1955; assigned to American Cyanamid Co.

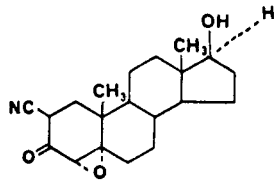
TRILOSTANE

Therapeutic Function: Corticosteroid antagonist

Chemical Name: 2α-Cyano-4α,5α-epoxyandrostan-17β-ol-3-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 13647-35-3

Trade Name	Manufacturer	Country	Year Introduced
Modrenal	Sterling Winthrop	U.K.	1980
Winstan	Winthrop	W. Germany	1982

Raw Materials

17β-Acetoxy-4-androsteno[2,3-d] isoxazole
Maleic anhydride
Hydrogen peroxide
Sodium methoxide

Manufacturing Process

(A) 17β-acetoxy-4α,5α-epoxyandrostano[2,3-d] isoxazole, melting point 228.6°C to 229.8°C (corrected) recrystallized from a benzene-methanol mixture, $[\alpha]_D^{25}$ = +76.5°C (1% in chloroform), was prepared by treating 17β-acetoxy-4-androsteno[2,3-d] isoxazole with maleic anhydride and hydrogen peroxide in methylene dichloride solution.

(B) 2α-cyano-4α,5α-epoxandrostan-17β-ol-3-one was prepared by treating 17β-acetoxy-4α, 5α-epoxyandrostano[2,3-d] isoxazole with sodium methoxide, and was obtained in the form of tan crystals, melting point 257.8°C to 270.0°C (decomposition) (corrected) when recrystallized from a pyridine-dioxane mixture.

References

Merck Index 9505
DFU 6 (8) 494 (1981)
OCDS Vol. 2 p. 158 (1980)
DOT 17 (5) 203 (1981)
I.N. p. 979
Clinton, R.O. and Manson, A.J.; U.S. Patent 3,296,255; January 3, 1967; assigned to Sterling Drug, Inc.

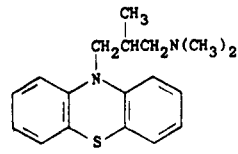
TRIMEPRAZINE

Therapeutic Function: Antipruritic

Chemical Name: N,N,β-Trimethyl-10H-phenothiazine-10-propanamine

Common Name: Alimemazine

Structural Formula:



Chemical Abstracts Registry No.: 84-96-8

Trade Name	Manufacturer	Country	Year Introduced
Temaril	SKF	U.S.	1958
Theralene	Theraplix	France	1958
Alimezine	Daiichi	Japan	–
Nedeltran	Bournonville	Belgium	–
Panectyl	Rhone-Poulenc	Canada	–
Repeltin	Bayer	W. Germany	–
Vallergan	May & Baker	U.K.	–
Variargil	Rhodia Iberica	Spain	–

Raw Materials

Phenothiazine
Sodium amide
1-Chloro-2-methyl-3-dimethylaminopropane

Manufacturing Process

95% sodamide (2.77 grams) is added to a solution of phenthiazine (9.6 grams) in xylene (140 cc) at a temperature of 130°C and the mixture is heated with reflux for 2 hours.

A 0.61 N solution (90 cc) of 1-chloro-2-methyl-3-dimethylaminopropane in xylene is then added over 50 minutes and heating with reflux is continued for 20 hours. After cooling, the mixture is treated with water (40 cc) and N methanesulfonic acid (70 cc). The aqueous layer is washed with ether, treated with aqueous sodium hydroxide (density = 1.33; 10 cc) and extracted with ether.

The extract is dried over potassium carbonate and evaporated and the residue is distilled in vacuo. 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (12.6 grams) is collected, distilling between 150° and 175°C under a pressure of about 0.3 mm Hg. By dissolving this base in acetone and adding ethereal hydrogen chloride, a hydrochloride is obtained, MP 216° to 217°C.

References

Merck Index 9510
Kleeman & Engel p. 25
PDR p. 1727
OCDS Vol. 1 p. 378 (1977)
I.N. p. 55
REM p. 1130
Jacob, R.M. and Robert, J.G.; U.S. Patent 2,837,518; June 3, 1958; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

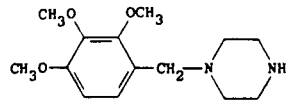
TRIMETAZIDINE

Therapeutic Function: Coronary vasodilator

Chemical Name: 1-[(2,3,4-Trimethoxyphenyl)methyl] piperazine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 5011-34-7; 13171-25-0 (Dihydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Vastarel	Biopharma	France	1963
Cartoma	Ohta	Japan	–
Coronanyl	Toho	Japan	–
Hiwell	Toa Eiyo	Japan	–
Lubomanil	Maruko	Japan	–
Sainosine	Nippon Chemiphar	Japan	–
Trimeperad	Kotobuki	Japan	–
Vassarin-F	Taiyo	Japan	–
Vastazin	Takeda	Japan	–
Yosimilon	Kowa Yakuhin	Japan	–

Raw Materials

2,3,4-Trimethoxybenzyl chloride
1-Formylpiperazine
Sodium carbonate

Manufacturing Process

Monoformylpiperazine is reacted molecule for molecule with 2,3,4-trimethoxybenzyl chloride in the presence of 1½ molecules of sodium carbonate and in suspension in ethyl alcohol, during 2 to 3 hours.

The reaction product is filtered and the filtrate is evaporated in vacuo to remove the alcohol. There remains an oily product from which the excess formyl-ethylenediamine is removed by distillation under 1 mm Hg pressure up to 125°C. The dark yellow, residual product is treated with 10% hydrochloric acid at 100°C for 12 hours to eliminate the formyl group; it is evaporated to a syrupy consistency and taken up with ethyl alcohol at the boiling point until complete miscibility is attained; it is then discolored over carbon, filtered and stored at low temperature.

The (2,3,4-trimethoxyphenyl)methylpiperazine hydrochloride precipitates as white needles; the precipitate is drained and washed with anhydrous sulfuric ether. Melting point: 222°C to 226°C.

References

Merck Index 9511
Kleeman & Engel p. 922
I.N. p. 980
Servier, J.; U.S. Patent 3,262,852; July 26, 1966; assigned to Biofarma S.A. (France)

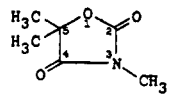
TRIMETHADIONE

Therapeutic Function: Anticonvulsant

Chemical Name: 3,5,5-trimethyl-2,4-oxazolidinedione

Common Name: Troxidone

Structural Formula:



Chemical Abstracts Registry No.: 127-48-0

Trade Name	Manufacturer	Country	Year Introduced
Tridione	Abbott	U.S.	1946
Trimethadione	Abbott	France	1960
Absentol	Nourypharma	Neth.	—
Epidione	Roger Bellon	France	—
Mino-Aleviatin	Dainippon	Japan	—
Trioxanona	Bama-Geve	Spain	—

Raw Materials

Ethyl α-hydroxyisobutyrate
Sodium
Ethanol
Urea
Methyl iodide

Manufacturing Process

To a cooled solution of 23 parts of sodium in 400 parts of dry ethanol are added 60 parts of dry urea and 132 parts of ethyl α-hydroxy-isobutyrate. The mixture is heated on a steam bath under reflux for about 16 hours and the liberated ammonia is removed from the solution by drawing a current of dry air through it at the boiling point. The solution of the sodium salt of 5,5-dimethyloxazolidine-2,4-dione so obtained is cooled and treated with 284 parts of methyl iodide. The mixture is allowed to stand at room temperature for 3 days, excess methyl iodide and ethanol are then removed by distillation under reduced pressure.

The residue is dissolved in ether and the solution is washed with sodium chloride solution and then with a little sodium thiosulfate solution. The ethereal solution is dried over sodium sulfate and ether removed by distillation. A yield of 108 parts of 3,5,5-trimethyloxazolidine-2,4-dione is obtained having a melting point of 45° to 46°C with slight softening at 43°C. This represents a 75% theory yield on the ethyl α-hydroxy-iso-butyrate taken. The product may be further purified by dissolving the minimum quantity of dry ether and cooling to -10°C. The product so obtained melts sharply at 45.5° to 46.5°C, according to U.S. Patent 2,559,011.

References

Merck Index 9512
Kleeman & Engel p. 922
PDR p. 554
OCDS Vol. 1 p. 232 (1977)
I.N. p. 980
REM p. 1082

Davies, J.S.H. and Hook, W.H.; U.S. Patent 2,559,011; July 3, 1951; assigned to British Schering Research Laboratories Limited, England
Spielman, M.A.; U.S. Patent 2,575,692; November 20, 1951; assigned to Abbott Laboratories

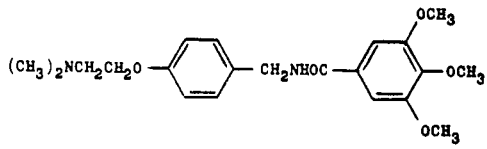
TRIMETHOBENZAMIDE HYDROCHLORIDE

Therapeutic Function: Antinauseant

Chemical Name: N-[(2-dimethylaminoethoxy)benzyl]-3,4,5-trimethoxybenzamide hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 554-92-7; 138-56-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tigan	Beecham	U.S.	1973
Hymetic	Hyrex	U.S.	1983
Ticon	Hauck	U.S.	1983
Ametik	Lafar	Italy	–
Anaus	Molteni	Italy	–
Anti-Vomit	Deva	Turkey	–
Contrauto	Aterni	Italy	–
Emedur	Dif-Dogu	Turkey	–
Ibikin	I.B.P.	Italy	–
Kantem	Kansuk	Turkey	–
Poligerim	Biotifar	Portugal	–
Stemetic	Legere	U.S.	–
Xametina	Zambeletti	Italy	–

Raw Materials

p-Hydroxybenzaldehyde
2-Dimethylaminoethyl chloride
3,4,5-Trimethoxybenzoyl chloride
Sodium methoxide
Hydrogen

Manufacturing Process

To 122 grams (1 mol) of p-hydroxybenzaldehyde in 1 liter of chlorobenzene were added 66 grams (1.04 mols) of sodium methoxide (85%) and 108 grams (1 mol) of 2-dimethylaminoethyl chloride. The mixture was stirred and refluxed for 15 hours, then cooled and the precipitated sodium chloride filtered off. The filtrate was concentrated at steam temperature under water vacuum and the residual oil was fractionated in high vacuum, to give 4-(2-dimethylaminoethoxy)benzaldehyde, $BP_{2.2}$ 145°C.

Two teaspoons of Raney nickel catalyst were added to a solution of 65.6 grams (0.34 mol) of 4-(2-dimethylaminoethoxy)benzaldehyde in 300 ml of 10% ammoniacal ethanol. The

mixture was hydrogenated at 80°C and a pressure of 1,000 psi. The catalyst was filtered off, the volatiles were distilled off and the residual oil was fractionated in high vacuum, to obtain 4-(2-dimethylaminoethoxy)benzylamine, $BP_{0.3}$ 120° to 123°C.

To 9.7 grams (0.05 mol) of 4-(2-dimethylaminoethoxy)benzylamine, dissolved in 100 ml of acetonitrile, was added all at once 12 grams (0.051 mol) of 3,4,5-trimethoxybenzoyl chloride, dissolved in 75 ml of acetonitrile. The mixture was stirred and refluxed for 8 hours, and then cooled. The crystalline solid, which had formed, was filtered off, washed with acetonitrile and recrystallized from acetonitrile, to give 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)benzylamine hydrochloride, MP 185° to 186°C.

References

Merck Index 9515
Kleeman & Engel p. 923
PDR pp. 665, 1033, 1606
OCDS Vol. 1 p. 110 (1977)
I.N. p. 980
REM p. 810
Goldberg, M.W. and Teitel, S.; U.S. Patent 2,879,293; March 24, 1959; assigned to Hoffmann-La Roche Inc.

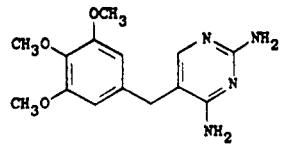
TRIMETHOPRIM

Therapeutic Function: Antibacterial (urinary)

Chemical Name: 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 738-70-5

Trade Name	Manufacturer	Country	Year Introduced
Eusaprim	Wellcome	Italy	1970
Bactrim	Roche	Italy	1970
Baktar	Shionogi	Japan	1976
Ipral	Squibb	U.K.	1979
Trimopam	Berk	U.K.	1979
Trimanyl	Tosse	W. Germany	1980
Syraprim	Wellcome	U.K.	1980
Proloprim	Burroughs Wellcome	U.S.	1980
Trimpex	Roche	U.S.	1980
Wellcoprim	Wellcome	France	1981
Trimopan	Farmitalia	Italy	1982
Monotrim	Gea	Switz.	1983
Cistal	Gamir	Spain	–
Comoxol	Squibb	U.S.	–
Cotrim	Lemmon	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Idotrim	Ferrosan	Denmark	–
Oratrim	Medica	Finland	–
Proloprim	Calmic	Canada	–
Septra	Burroughs Wellcome	U.S.	–
Tiempe	D.D.S.A.	U.K.	–
Trimanyl	Gea	Denmark	–
Trimecur	Leiras	Finland	–
Trimfect	Neofarma	Finland	–
Trimpex	Roche	U.S.	–
Triprim	Berk	U.K.	–

Raw Materials

β-Methoxypropionitrile
3,4,5-Trimethoxybenzaldehyde
Sodium
Guanidine

Manufacturing Process

6 grams (0.26 mol) sodium was dissolved in 300 ml methanol under stirring and refluxing. 47.5 grams (0.55 mol) β-methoxypropionitrile and 98 grams (0.5 mol) 3,4,5-trimethoxybenzaldehyde were added and the mixture refluxed gently for 4 hours. The mixture was then chilled and 150 ml of water was added. The product crystallized rapidly. Crystallization was allowed to proceed at 5° to 10°C under stirring for 1 hour. The product was filtered by suction and washed on the filter with 200 ml of 60% ice cold methanol. The crude material was air-dried and used for further steps without purification. It melted at 78° to 80°C. A pure sample, recrystallized from methanol, melted at 82°C. The yield of 3,4,5-trimethoxy-2'-methoxymethylcinnamonitrile was 92 grams, corresponding to 70% of the theory.

19 grams (0.83 mol) sodium was dissolved in 300 ml methanol, 106 grams of 3,4,5-trimethoxy-2'-methoxymethylcinnamonitrile was added and the mixture gently refluxed for 24 hours. The solution, which had turned brown, was poured into 1 liter of water and the precipitated oil extracted repeatedly with benzene. The combined benzene layers (500 to 700 ml) were washed 3 times with 500 ml of water, the benzene removed by evaporation in a vacuum from a water bath, and the brown residual oil distilled in vacuo, boiling point 215° to 225°C/11 mm. The clear, viscous oil, 3,4,5-trimethoxy-2'-cyano-dihydrocinnamaldehyde dimethyl acetal, weighed 83 grams (71% of the theory), and showed a n_D^{23} = 1.5230. It solidified upon standing. A sample recrystallized from methanol melted at 69° to 70°C and showed a strong melting point depression with the starting material; n_D^{25} = 1.5190.

31.5 grams (0.107 mol) 3,4,5-trimethoxy-2'-cyano-dihydrocinnamaldehyde dimethyl acetal was refluxed with methanolic guanidine solution (200 ml containing 0.25 mol of guanidine) for 2 hours. The methanol completely distilled off under stirring, finally from a bath of 110° to 120°C until the residue solidified completely to a yellowish crystalline mass. After allowing to cool, it was slurried with 100 ml of water and collected by vacuum filtration and dried. The yield of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine amounted to 28 grams (91% of the theory). The material showed the correct melting point of 199° to 200°C and was, however, yellowish discolored.

20 grams of the above product was added to 30 ml of 3 N aqueous sulfuric acid at 60°C under stirring. The solution was chilled under stirring to 5° to 10°C. The crystalline sulfate was collected by vacuum filtration and washed on the filter twice with 10 ml of cold 3 N aqueous sulfuric acid each time. From the filtrate there was recovered 1.3 grams. (6.5%) of discolored material melting at 195° to 196°C and which can be added to subsequent purification batches.

The sulfate on the filter was dissolved in 200 ml of hot water, the solution charcoaled hot, and the product precipitated from the clear colorless filtrate by the gradual addition of a

solution of 20 grams of sodium hydroxide in 40 ml of water under chilling. The precipitate was filtered by suction and washed thoroughly with water on the filter. The white material, 17.5 grams (88%) showed the correct melting point of 200° to 201°C, according to U.S. Patent 3,341,541.

References

Merck Index 9516
Kleeman & Engel p. 923
PDR pp. 673, 759, 830, 993, 1034, 1474, 1505, 1606, 1738
OCDS Vol. 1 p. 262 (1977) & 2, 302 (1980)
DOT 5 (3) 113 (1969); 12 (9) 377 (1976) & 16 (4) 128 (1980)
I.N. p. 980
REM p. 1215
Stanbuck, P. and Hood, H.M.; U.S. Patent 3,049,544; August 14, 1962; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Hoffer, M.; U.S. Patent 3,341,541; September 12, 1967; assigned to Hoffmann-La Roche Inc.

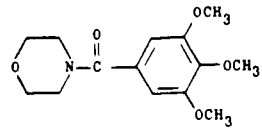
TRIMETOZINE

Therapeutic Function: Sedative

Chemical Name: 4-(3,4,5-Trimethoxybenzoyl)morpholine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 635-41-6

Trade Name	Manufacturer	Country	Year Introduced
Opalene	Theraplix	France	1966
Trioxazine	Labatec	Italy	1971

Raw Materials

3,4,5-Trimethoxybenzoyl chloride
Morpholine

Manufacturing Process

46 g 3,4,5-trimethoxybenzoyl chloride are dissolved in 300 ml anhydrous benzene and 25 g triethylamine and thereafter 19 g anhydrous morpholine are added in small portions with ice-cooling. The solution is boiled for 2 hours under reflux. The precipitate is filtered off, and the solution is washed with dilute sulfuric acid, then with sodium hydrogen carbonate solution and finally with water, and then evaporated. The residual yellow oil soon crystallizes; the crystalline mass of the desired material is taken up with ether, filtered and then recrystallized from 90% ethanol, from which it separates in prisms. It is slightly soluble in water. Yield: 80%, melting point 120°C to 122°C.

References

Merck Index 9527
Kleeman & Engel p. 927
OCDS Vol. 2 p. 94 (1980)
DOT 3 (3) 106 (1967)
I.N. p. 981
Egyesult Gyogyszer és Tapszer Gyar; British Patent 872,350; July 5, 1961

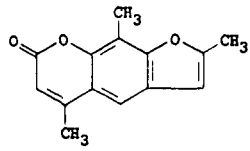
TRIOXSALEN

Therapeutic Function: Pigmentation enhancer

Chemical Name: 2,5,9-trimethyl-7H-furo[3,2-g] benzopyran-7-one

Common Name: 2',4,8-trimethylpsoralen

Structural Formula:



Chemical Abstracts Registry No.: 3902-71-4

Trade Name	Manufacturer	Country	Year Introduced
Trisoralen	Elder	U.S.	1965
Trisoralen	Santen	Japan	1969
Trisoralen	Farmochimica	Italy	1970
Trisoralen	Panpharma	Switz.	1981
Levrison	Rovi	Spain	–

Raw Materials

Ethyl acetoacetate
Allyl bromide
Bromine
Hydrogen chloride
2-Methyl resorcinol
Acetic anhydride
Sodium

Manufacturing Process

(A) Preparation of 7-Hydroxy-4,8-Dimethylcoumarin: Chilled ethyl acetoacetate (157 ml, 1.20 mols) followed by 2-methyl-resorcinol (130 g, 1.04 mols) was dissolved in well-stirred concentrated sulfuric acid (600 ml) at such a rate as to keep the temperature below 10°C (ice bath). The stirred solution was allowed to warm gradually and after 3 hours was added to water (ca 8 liters) with mechanical stirring. The product was collected, washed twice with water, and dried at 70° to 80°C until the first sign of darkening. Yield 191.3 g (95.4%). Recrystallization from aqueous ethanol gave 7-hydroxy-4,8-dimethylcoumarin as colorless needles, MP 260.5° to 261°C. In dilute sodium hydroxide, the compound gives a yellow solution which exhibits blue fluorescence.

(B) Preparation of 7-Allyloxy-4,8-Dimethylcoumarin: 7-Hydroxy-4,8-dimethylcoumarin (191.3 g, 1.01 mols), anhydrous potassium carbonate (604 g, 4.37 mols), and allyl bromide (578 ml, 6.22 mols) were refluxed overnight in acetone (ca 3 liters) with mechanical stirring. The reaction mixture was concentrated nearly to dryness on a steam bath under re-

duced pressure, water (ca 8 liters) was added, and the product was collected by filtration. It was washed with 5% NaOH and water (ca 1.5-liter portions) and was dried in a vacuum desiccator. The dry solid was washed with petroleum ether (30° to 60°C) to remove excess allyl bromide. Removal of the petroleum ether under reduced pressure left 210.0 g (90.7% yield) of product. The 7-allyloxy-4,8-dimethylcoumarin was crystallized from aqueous ethanol as colorless needles, MP 108° to 109°C.

(C) Preparation of 6-Allyl-7-Hydroxy-4,8-Dimethylcoumarin: 7-Allyloxy-4,8-dimethylcoumarin (195.0 g, 0.84 mol) was heated (oil bath) to 215±4°C (reaction mixture temperature) for 3 hours and was then poured into absolute alcohol (ca 1.5 liters). Activated carbon (Norite) (19.5 g) was added, and the solution was heated to boiling, filtered, and diluted with excess water (ca 12 liters). The product was collected by filtration and partially dried at 70°C for 6 hours. 6-Allyl-7-hydroxy-4,8-dimethylcoumarin was obtained as pale yellow microcrystalline prisms, MP 166° to 168°C, by two recrystallizations from aqueous ethanol of a portion of the partially dried solid. The remaining partially dried solid was used in the next step.

(D) Preparation of 7-Acetoxy-6-Allyl-4,8-Dimethylcoumarin: A solution of the partially dried 6-allyl-7-hydroxy-4,8-dimethylcoumarin obtained in the previous step, acetic anhydride (915 ml, 9.7 mols) and fused sodium acetate (2 g) was refluxed for 4 hours and added to water (ca 8 liters) with mechanical stirring. After excess acetic anhydride had decomposed, the 7-acetoxy-6-allyl-4,8-dimethylcoumarin was collected by filtration, dried, and recrystallized from absolute alcohol, MP 144.5° to 145.5°C. Yield 145.4 g (63.8%, based on 7-allyloxy-4,8-dimethylcoumarin).

(E) Preparation of 7-Acetoxy-6-(2',3'-Dibromopropyl)-4,8-Dimethylcoumarin: 7-Acetoxy-6-allyl-4,8-dimethylcoumarin (145.4 g, 0.534 mol) was dissolved in chloroform (ca 800 ml). The stirred solution was cooled in an ice bath and bromine (85.2 g, 0.534 mol) in chloroform (200 ml) was added at such a rate as to keep the temperature below 25°C. Evaporation of chloroform on the steam bath left an off-white residue of the crude dibromide. Yield 230.6 g (quantitative). 7-Acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin was crystallized from ethanol as colorless prisms, MP 141.5° to 142.5°C.

(F) Preparation of 2',4,8-Trimethylpsoralen: Crude 7-acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin (245.7 g, 0.57 mol) was refluxed for 1¾ hours with a stirred solution of sodium (65.4 g, 2.85 mols) in a magnesium-dried ethanol (2.1 liters). After standing at room temperature for 15 minutes, the reaction mixture was poured into a stirred mixture of ice (8,000 g) and a 3.5% HCl (8 liters). Twelve hours later, the precipitate had coagulated and was collected by filtration; it was thoroughly washed with successive 3-liter portions of 5% NaOH, water, 0.5% HCl, and water.

After partial drying at 60°C for 5 hours, the crude trimethylpsoralen material was thoroughly dried in a vacuum desiccator. Yield 110.1 g (85%). Fractional crystallization, using activated carbon (Norite) (30.8 g), from mixtures of chloroform and petroleum ether (30° to 60°C) and finally from chloroform alone gave colorless prisms of 2',4,8-trimethylpsoralen, MP 234.5° to 235°C. Yield 61.8 g (48%).

References

Merck Index 9538
PDR p. 871
OCDS Vol. 1 p. 334 (1977)
I.N. p. 982
REM p. 790
Kaufman, K.D.; U.S. Patent 3,201,421; August 17, 1965

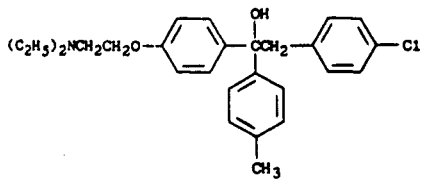
TRIPARANOL

Therapeutic Function: Antilipemic

Chemical Name: 4-Chloro-α-[4-[2-(diethylamino)ethoxy] phenyl] -α-(4-methylphenyl)benzene ethanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 78-41-1

Trade Name	Manufacturer	Country	Year Introduced
Mer-29	Merrell National	U.S.	1960

Raw Materials

4-Hydroxy-4-methylbenzophenone
β-Diethylaminoethyl chloride
Magnesium
Sodium methoxide
p-Chlorobenzyl chloride

Manufacturing Process

4-(β-diethylaminoethoxy)-4-methylbenzophenone was prepared as follows: a mixture of 200 g of 4-hydroxy-4-methylbenzophenone, 55 g of powdered sodium methoxide and 400 ml of ethanol was stirred for 30 minutes. A solution of 150 g of β-diethylaminoethyl chloride in 300 ml of toluene was added and the mixture was refluxed four hours. The solvent was removed, the residue was taken up in ether, extracted with 5% NaOH solution, twice with water, the ether was removed and the residue was distilled. The product was obtained as an oil boiling at 232°C at 0.6 mm.

1 liter of a 0.45 N ethereal solution of p-chlorobenzyl magnesium chloride was added in 30 minutes to a stirred solution of 104 g (0.35 mol) of 4-(β-diethylaminoethoxy)-4-methylbenzophenone in 400 ml of dry ether. After stirring an additional hour, the mixture was decomposed by pouring onto 1 liter of cold 10% ammonium chloride solution, the ether solution was washed with water, and the ether was replaced with hot isopropanol containing a trace of ammonia. 1-[p-(β-diethylaminoethoxy)phenyl]-1-phenyl-2-p-tolyl-2-p-chloroethanol separated as white crystals, melting at 104°C to 106°C.

References

Merck Index 9541
I.N. p. 982
Allen, R.E., Palopoli, F.P., Schumann, E.L. and Van Campen, M.G. Jr.; U.S. Patent 2,914,562; November 24, 1959; assigned to Wm. S. Merrell Co.

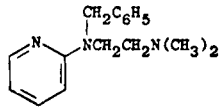
TRIPELENNAMINE

Therapeutic Function: Antihistaminic

Chemical Name: N,N-dimethyl-N'-(phenylmethyl)-N'-2-pyridinyl-1,2-ethanediamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 91-81-6; 154-69-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Pyribenzamine	Ciba	U.S.	1946
PBZ-SR	Ciba Geigy	U.S.	1977
Anhistamin	Pharmachim	Bulgaria	–
Antamine	Teva	Israel	–
Antiallergicum Medivet	Medivet	Switz.	–
Sedilene	Montefarmaco	Italy	–

Raw Materials

α-Aminopyridine
Dimethylaminochloroethane
Benzaldehyde
Sodium amide

Manufacturing Process

46 g of α-benzylaminopyridine in 50 cc of dry toluene are heated to 80°C [the α-benzylaminopyridine may be obtained either according to the method of Tchitchibabine and Knunjanz, *Berichte,* 64, 2839 (1931), which consists in warming α-aminopyridine with benzaldehyde in formic acid, or alternatively by the action of benzyl chloride on sodio-α-aminopyridine]. To the toluene solution there are added gradually 9.5 g of 85% sodamide. After evolution of ammonia, the major part of the toluene is distilled off; into the pasty mass which remains there are poured 120 cc of an ethereal solution of 27 g of dimethylaminochloroethane.

The mixture is heated until the temperature reaches 140°C, the ether distilling out, then finally heated under reduced pressure (150 mm Hg) for ½ hour. The mass is taken up with dilute hydrochloric acid and ether, neutralized at pH 7, and α-benzylaminopyridine separates. After making alkaline, using excess of potash, it is extracted with benzene, dried and distilled. The product thereby obtained, dimethylamino-ethyl-N-benzyl-N-α-aminopyridine, boils at 135° to 190°C/1.7 mm, according to U.S. Patent 2,502,151.

References

Merck Index 9542
Kleeman & Engel p. 928
PDR pp. 830, 898
OCDS Vol. 1 p. 51 (1977)
I.N. p. 983
REM p. 1130
Djerassi, C., Huttrer, C.P. and Scholz, C.R.; U.S. Patent 2,406,594; August 27, 1946; assigned to Ciba Pharmaceutical Products Incorporated
Horclois, R.J.; U.S. Patent 2,502,151; March 28, 1950; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

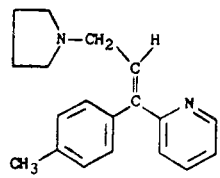
TRIPROLIDINE

Therapeutic Function: Antihistaminic

Chemical Name: (E)-2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl] pyridine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 486-12-4; 550-70-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Actidil	Burroughs Wellcome	U.S.	1958
Actidilon	Wellcome	France	1965
Bayidyl	Bay	U.S.	1983
Actifed	Burroughs Wellcome	U.S.	–
Actiphyll	Gayoso Wellcome	Spain	–
Entra	Wellcome-Tanabe	Japan	–
Histradil	Trima	Israel	–
Pro-Actidil	Burroughs Wellcome	U.K.	–
Pro-Entra	Wellcome-Tanabe	Japan	–
Triafed	Schein	U.S.	–
Tripodrine	Danbury	U.S.	–
Venen	Tanabe	Japan	–

Raw Materials

4-Methylacetophenone
Pyrrolidine
2-Bromopyridine
Paraformaldehyde
Lithium

Manufacturing Process

4-Methylacetophenone is first reacted with paraformaldehyde and then with pyrrolidine to give p-methyl-ω-pyrrolidinopropiophenone.

Atomized lithium (26 g, 3.75 mols) and sodium-dried ether (200 cc) are placed in a 3-liter, 3-necked flask fitted with a Herschberg stirrer, thermometer pocket and a water condenser closed by a calcium chloride tube. A slow stream of dry nitrogen is blown through the flask, which is cooled to -10°C and n-butyl chloride (138 g, 156 cc, 1.5 mols) is run in with rapid stirring; the mixture is stirred for a further 30 minutes, and then cooled to -60°C

2-Bromopyridine (193 g, 1.22 mols) is then added dropwise over 20 minutes, the temperature of the reaction mixture being maintained at -50±2°C. The mixture is stirred for 10 minutes at -50°C and p-methyl-ω-pyrrolidinopropiophenone (112.5 g, 0.5 mol) in dry benzene is then added dropwise over ca 30 minutes, at a temperature of -50±2°C. The mixture is stirred for a further 2 hours, the temperature being allowed to rise to -30°C but no higher.

The mixture is poured onto excess ice, acidified with concentrated hydrochloric acid, the ether layer separated and extracted with water (1 x 200 cc). The combined aqueous extracts are washed with ether (1 x 200 cc) basified with 0.880 ammonia and extracted with chloroform (3 x 350 cc); the extract is washed with water (2 x 100 cc), dried over sodium sulfate, evaporated, and the residue extracted with boiling light petroleum (BP 60° to 80°C; 10 volumes), filtered hot and evaporated to dryness. The residue is recrystallized from alcohol to give a cream solid (119 g, 80%), MP 117° to 118°C. Recrystallization gives 1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidonopropan-1-ol, MP 119° to 120°C.

1-(4-Methylphenyl)-1-(2-pyridyl)-3-pyrrolidinopropan-1-ol (10.0 g) is heated in a steam bath for 30 minutes with 85% aqueous sulfuric acid (30 cc). The solution is then poured onto crushed ice, excess of ammonia solution added and the liberated oil extracted with light petroleum (BP 60° to 80°C). The extract is dried over anhydrous sodium sulfate and the solvent evaporated to leave an amber syrup (8.8 g) consisting of the cis and trans isomers of 1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidinoprop-1-ene as described in U.S. Patent 2,712,023. The isomers may be separated by base exchange chromatography. The 4-methyl-ω-pyrrolidinopropiophenone required as the starting product for the preparation of the carbinol is prepared by the Mannich reaction (Blicke, *Organic Reactions,* 1942, vol 1, p 303; Adamson & Billinghurst, *Journal of the Chemical Society,* 1950, 1039) from 4-methylacetophenone and pyrrolidine. The hydrochloride has a MP of 170°C with decomposition.

References

Merck Index 9552
Kleeman & Engel p. 929
PDR pp. 731, 830, 993, 1569, 1606, 1999
OCDS Vol. 1 p. 78 (1977)
I.N. p. 983
REM p. 1130
Adamson, D.W.; U.S. Patent 2,712,020; June 28, 1955; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.
Adamson, D.W.; U.S. Patent 2,712,023; June 28, 1955; assigned to Burroughs Wellcome & Co. (U.S.A.) Inc.

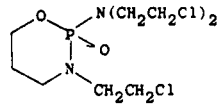
TROFOSFAMIDE

Therapeutic Function: Cancer chemotherapy

Chemical Name: N,N,3-tris(2-chloroethyl)-tetrahydro-2H-1,3,2-oxaphosphorin-2-amine-2-oxide

Common Name: Trophosphamide

Structural Formula:



Chemical Abstracts Registry No.: 22089-22-1

Trade Name	Manufacturer	Country	Year Introduced
Ixoten	Asta	W. Germany	1973
Ixoten	Schering	Italy	1975

Raw Materials

N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride
N-(2-Chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride
Triethylamine

Manufacturing Process

259 g (1 mol) of N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride, 209 g (1.2 mols) of N-(2-chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride (crude), 1,000 cc of ethylene

dichloride and 344 g (3.4 mols) of triethylamine are the reactants. N,N-bis-(2-chloroethyl)-phosphoric acid amide dichloride is dissolved in the methylene dichloride. N-(2-chloroethyl)-N-(3-hydroxypropyl)-amine hydrochloride is suspended in this solution and triethylamine is added thereto dropwise with stirring. The temperature of the solution rises to boiling. After the termination of the addition, the mixture is heated to boiling for another 6 hours. Thereafter, the reaction mixture is cooled down and allowed to stand overnight at about 0°C. The precipitated triethylamine hydrochloride is filtered off with suction. The resulting solution is evaporated, the residue (about 370 g) is triturated with about 3.2 liters of ether and is heated to boiling for a short period of time.

The ethereal solution is decanted from the insolubles (about 90 g). The solution is rendered to pH 6.5 to 7 by the addition of ethereal hydrochloric acid and then is filtered over charcoal and thereafter is evaporated. During evaporation, the temperature should not rise above 40°C. The residue is dissolved in ether and in an amount corresponding to half of its weight (240 g of residue, dissolved in 120 cc of ether), the ethereal solution is cooled to -5°C and is inoculated. After standing for 25 hours, 140 g have been separated by crystallization. After separation by filtration with suction, the mother liquor is diluted with ether to 5 times its volume, the solution is filtered over charcoal, is again evaporated and the residue is again dissolved in a volume corresponding to half of the weight of the residue. Another cooling to -5°C and inoculation produces further 18 g of the desired compound. MP: 50° to 51°C. Total yield: 161 g (50% of the theoretical).

References

Merck Index 9571
Kleeman & Engel p. 930
OCDS Vol. 3 p. 161 (1984)
DOT 9 (12) 502 (1973) & 13 (3) 118 (1977)
I.N. p. 985
Asta-Werke AG Chemische Fabrik, Germany; British Patent 1,188,159; April 15, 1970
Arnold, H., Brock, N., Bourseaux, F. and Bekel, H.; U.S. Patent 3,732,340; May 8, 1973; assigned to Asta-Werke AG Chemische Fabrik

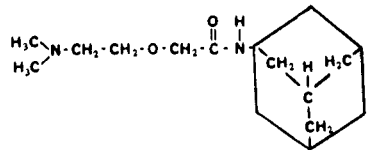
TROMANTIDINE HYDROCHLORIDE

Therapeutic Function: Antiviral

Chemical Name: N-(2-Dimethylamino-ethoxy)-acetyl-aminoadamantane(1) hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 41544-24-5; 53783-83-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Viru-Merz	Merz	W. Germany	1973
Viruserol	Zyma	Italy	1972

Raw Materials

Chloroacetyl chloride
Adamantane
Dimethylaminoethanol
Sodium

Manufacturing Process

Adamantane is first reacted with chloroacetyl chloride to give chloroacetylaminoadamantane.

2.3 g Na (0.1 g-atom) were dissolved in 75 ml dimethylamino-ethanol. Then the excess alcohol was distilled off completely and the sodium salt developed was dried in a vacuum. After drying, the salt was dissolved in about 200 ml xylene. To this solution, 22.8 g (0.1 mol) chloroacetylaminoadamantane were added, heated for 10 hours under reflux in a 250-ml round-bottomed flask with a reflux cooler, and the sodium chloride developed subsequently filtered off.

Next the xylene was distilled away, the liquid residue dissolved in about 80 ml carbon tetrachloride and the hydrochloride precipitated through introduction of hydrochloric acid gas. The hydrochloride was dissolved in about 100 ml acetone and the solvent subsequently distilled away, whereby excess hydrochloric acid passed over with it. This operation was repeated until no excess acid was present.

A large excess of petroleum ether was added in a 500-ml three-necked flask provided with a stirrer and reflux cooler, to a concentrated acetonic solution of the hydrochloride and stirred for at least 1 hour, whereby the desired substance was deposited in a crystalline form. Finally, the substance was filtered away and dried in a desiccator. 14 g of the substance (15% of theory) were obtained.

References

Merck Index 9574
Kleeman & Engel p. 930
DOT 10 (3) 105 (1974)
I.N. p. 985
Scherm, A. and Peteri, D.; U.S. Patent 3,705,194; December 5, 1972; assigned to Merz and Co., Chemische Fabrik

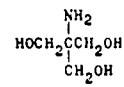
TROMETHAMINE

Therapeutic Function: Antacid

Chemical Name: 2-Amino-2-hydroxymethyl-1,3-propanediol

Common Name: Trometamol

Structural Formula:



Chemical Abstracts Registry No.: 77-86-1

Trade Name	Manufacturer	Country	Year Introduced
Trisaminol	Bellon	France	1964
In Tham-E	Abbott	U.S.	1965

Trade Name	Manufacturer	Country	Year Introduced
Tham	Otsuka	Japan	1969
Thamesol	Baxter	Italy	1970
Addex-Tham	Pharmacia	Sweden	–
Alcaphor	Bellon	France	–
Apiroserum	Ibys	Spain	–
Basionic	Smith Kline-R.I.T.	Belgium	–
Buffer	Pages Maruny	Spain	–
Thamacetat	Bellon	France	–
Trizma	Sigma	U.S.	–

Raw Materials

Nitromethane
Formaldehyde
Hydrogen

Manufacturing Process

Nitromethane is reacted with formaldehyde to give tris(hydroxymethyl)nitromethane in an initial step. This intermediate may be reduced by catalytic hydrogenation (U.S. Patent 2,174,242) or by electrolytic reduction (U.S. Patent 2,485,982).

References

Merck Index 9575
DOT 1 (4) 139 (1965)
I.N. p. 986
REM p. 836
Hass, H.B. and Vanderbilt, B.M.; U.S. Patent 2,174,242; September 26, 1939; assigned to Purdue Research Foundation
McMillan, G.W.; U.S. Patent 2,485,982; October 25, 1949; assigned to Commercial Solvents Corporation

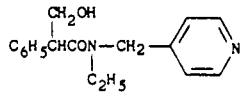
TROPICAMIDE

Therapeutic Function: Anticholinergic (ophthalmic)

Chemical Name: N-ethyl-α-(hydroxymethyl)-N-(4-pyridinylmethyl)benzeneacetamide

Common Name: N-ethyl-N-(γ-picolyl)tropamide

Structural Formula:



Chemical Abstracts Registry No.: 1508-75-4

Trade Name	Manufacturer	Country	Year Introduced
Mydriacyl	Alcon	U.S.	1959
Mydriaticum	MSD-Chibret	France	1960
Mydrin	Santen	Japan	–
Mydrum	Ankerwerk	E. Germany	–
Tropimil	Farmigea	Italy	–
Tryptar	Armour	U.S.	–
Visumidriatic	I.S.F.	Italy	–

Raw Materials

Ethyl amine
γ-Chloromethyl pyridine hydrochloride
Acetyltropic acid chloride
Hydrogen chloride

Manufacturing Process

A solution of 82 parts by weight of γ-chloromethyl-pyridine-hydrochloride in 60 parts of water is added dropwise, at 0° to 5°C, to 250 parts by weight of a 50% aqueous ethyl amine solution. The mixture is stirred for 1 hour at 60°C, whereupon it is cooled down and separated in the cold with solid potassium hydroxide. The oil formed is separated off, dried over potassium hydroxide and distilled. The ethyl-(γ-picolyl)-amine formed boils over at 103° to 104°C under a pressure of 13 mm Hg. Its dihydrochloride melts at 198° to 200°C.

To a mixture of 48.7 parts by weight of ethyl-(γ-picolyl)-amine and 36 parts by weight of dry pyridine in 220 parts by weight of dry chloroform is slowly added, while stirring and cooling with ice water, crude acetyltropic acid chloride prepared from 60 parts by weight of tropic acid. To complete the reaction, the mixture is stirred for one additional hour at 23°C. Thereupon the chloroform solution is diluted with 200 parts by weight of ether and agitated with 3 N hydrochloric acid. The weakly Congo acid solution is heated for 1 hour in a steam bath, the acetyl group of the reaction product being thereby split off, and the mixture is filtered over charcoal.

Upon adding concentrated ammonia in excess, the condensation product separates and is taken up in chloroform. The chloroform solution is dried and distilled, the tropic acid N-ethyl-N-(γ-picolyl)-amide being thereby obtained in the form of a thick oil, which crystallizes after prolonged time and which then melts at 96° to 97°C.

References

Merck Index 9585
Kleeman & Engel p. 932
DOT 16 (3) 89 (1980)
I.N. p. 986
REM p. 918
Rey-Bellet, G. and Spiegelberg, H.; U.S. Patent 2,726,245; December 6, 1955; assigned to Hoffmann-LaRoche Inc.

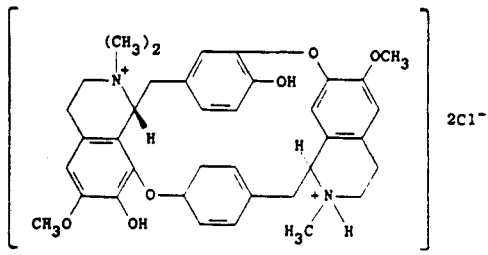
TUBOCURARINE CHLORIDE

Therapeutic Function: Skeletal muscle relaxant

Chemical Name: 7',12'-Dihydroxy-6,6'-dimethoxy-2,2',2'-trimethyl-tubocuraranium chloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 6533-76-2

Trade Name	Manufacturer	Country	Year Introduced
Mecostrin	Squibb	U.S.	1946
Amelizol	Yoshitomi	Japan	–
Curarin	Asta	W. Germany	–
Introcortin T	Squibb	Italy	–
Jexin	Duncan Flockhart	U.K.	–
Metubine	Lilly	U.S.	–
Relvene	Pharmascience	U.S.	–
Tubadil	Endo	U.S.	–
Tubocuran	N.D. & K.	Denmark	–

Raw Materials

Chondrodendron tomentosum plant
Picric acid
Hydrogen chloride

Manufacturing Process

The initial step involves extraction of the stems and bark of the plant *Chondrodendron tomentosum* with water as the solvent.

Producing substantially pure d-tubocurarine chloride essentially comprises treating with picric acid the quaternary-base fraction of a crude curare of the curarine type, hydrolyzing the resulting picrate in an emulsion of hydrochloric acid and a water-immiscible organic solvent for picric acid, recovering crystalline d-tubocurarine chloride from the aqueous phase, dissolving the d-tubocurarine chloride in a minimum of hot water, allowing the solution to stand at room temperature until the bulk of the d-tubocurarine chloride precipitates, adding sufficient concentrated hydrochloric acid to bring the HCl content up to about 6%, and refrigerating the solution.

References

Merck Index 9608
Kleeman & Engel p. 934
I.N. 988
REM p. 924
Bashour, J.T.; U.S. Patent 2,409,241; October 15, 1946; assigned to E.R. Squibb & Sons

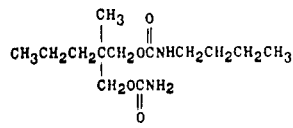
TYBAMATE

Therapeutic Function: Tranquilizer

Chemical Name: Butylcarbamic acid 2-[[(aminocarbonyl)oxy] methyl]-2-methylpentyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 4268-36-4

Trade Name	Manufacturer	Country	Year Introduced
Solacen	Wallace	U.S.	1965
Tybatran	Robins	U.S.	1967
Effisax	Maggioni	Italy	–
Nospan	Johnsons	Sweden	–

Raw Materials

Diethylmethyl propylmalonate
Sulfuric acid
Butylamine
Lithium aluminum hydride
Phosgene
Urethane

Manufacturing Process

Diethylmethyl propylmalonate is reacted with $LiAlH_4$, then H_2SO_4 to give 2-methyl-2-propyl-1,3-propanediol. That is reacted with phosgene in toluene to give the chlorocarbonate which is in turn reacted with butylamine to give N-butyl-2-methyl-2-propyl-3-hydroxy-propyl carbamate.

22.1 parts of N-butyl-2-methyl-2-propyl-3-hydroxy-propyl carbamate and 9.8 parts of urethane are dissolved in 300 parts of anhydrous xylene in a suitable vessel equipped with an efficient distillation column. Xylene is distilled to remove traces of water from the mixture. 2.3 parts of aluminum isopropylate are added and distillation is continued until substantially the theoretical quantity of ethanol has been distilled at about 78°C. The reaction mixture is then freed from xylene by distillation under reduced pressure. Approximately 100 parts of water are added and the mixture again freed of solvent by distillation under reduced pressure. 100 parts of trichloroethylene are added, the solution filtered to remove insoluble matter and the solution freed of solvent by evaporation. The residual oil is purified by molecular distillation at a pressure of about 0.01 mm. 8.7 parts (35% of theoretical yield) of purified N-butyl-2-methyl-2-propyl-1,3-propanediol dicarbamate are obtained.

References

Merck Index 9628
Kleeman & Engel p. 935
OCDS Vol. 2 p. 22 (1980)
DOT 3 (3) 101 (1967)
I.N. p. 989
REM p. 1074
Berger, F.M. and Ludwig, B.J.; U.S. Patent 2,937,119; May 17, 1960; assigned to Carter Products, Inc.

TYLOXAPOL

Therapeutic Function: Bronchodilator

Chemical Name: 4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and ethylene oxide

Common Name: –

Structural Formula: See chemical name

Chemical Abstracts Registry No.: 25301-02-4

Trade Name	Manufacturer	Country	Year Introduced
Superinone	Winthrop	U.S.	1953
Alevaire	Breon	U.S.	1953
Lacermucin	Lacer	Spain	–
Tacholiquin	Benechemie	W. Germany	–
Triton WR	Rohm & Haas	U.S.	–

Raw Materials

α,α,γ,γ-Tetramethylbutylphenol
Formaldehyde
Ethylene oxide

Manufacturing Process

Step 1: Into a 3-necked flask equipped with thermometer, mechanical agitator, and reflux condenser was charged the following: 412 g of α,α,γ,γ-tetramethylbutylphenol, 162 g of a 37% aqueous solution of formaldehyde, and 27.6 g of water. The mixture was agitated and heated to a temperature of 90°C. At this point, 246 g of oxalic acid and 0.92 g of Twitchell's reagent dissolved in 10 g of water were added. While being agitated, the reaction mixture was refluxed for 6 hours. 200 g of water and 384 g of toluene were added, and refluxing was continued for an hour.

Agitation was stopped and the contents of the flask were removed to a separatory funnel. The aqueous and resinous layers were separated and the solvent was removed from the resinous layer by vacuum distillation. After the removal of the solvent, heating at a reduced pressure of 1.5 to 2.5 mm and at a temperature of 245° to 250°C was continued for 4½ hours. The condensate then had a viscosity of 4.0 poises when measured as a 60% solution in toluene and, on cooling, solidified to a brittle mass.

Step 2: A mixture of 118 parts of the product of Step 1, having hydroxyl number of 260, 2 parts of solid NaH, and 100 parts of toluene was heated to 125° to 150°C in an autoclave. Ethylene oxide was added slowly over a period of 2½ hours until 261 parts of ethylene oxide were absorbed. This corresponds to 11 mols of ethylene oxide per mol of phenol in the product of Step 1. The toluene was then removed by steam distillation and the water by vacuum distillation at 10°C. The product was obtained as a viscous paste having a corrected hydroxyl number of 97. It was readily soluble in water and had marked detergent properties.

References

Merck Index 9632
I.N. p. 990
REM p. 869
Bock, L.H. and Rainey, J.L.; U.S. Patent 2,454,541; assigned to Rohm & Haas Company

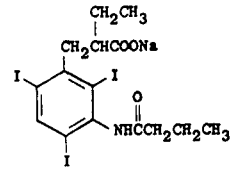
TYROPANOATE SODIUM

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: α-ethyl-2,4,6-triiodo-3-[(1-oxobutyl)amino] benzenepropanoic acid monosodium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 7246-21-1

Trade Name	Manufacturer	Country	Year Introduced
Bilopaque	Winthrop	U.S.	1972
Bilopaque	Winthrop	W. Germany	1977
Tyropaque	Torii	Japan	1979

Raw Materials

α-Ethyl-β-(aminophenyl)propionic acid
Iodine monochloride
Butyric anhydride
Sodium hydroxide

Manufacturing Process

A solution of 5.0 g of α-ethyl-β-(aminophenyl)propionic acid in 100 ml of water containing 5 ml of concentrated hydrochloric acid was added over a period of ½ hour to a stirred solution of 3.2 ml of iodine monochloride in 25 ml of water and 25 ml of concentrated hydrochloric acid heated to 60°C. After addition was complete, the heating was continued for ½ hour longer at 60° to 70°C. A black oil separated which gradually solidified. The mixture was then cooled and sodium bisulfite was added to decolorize. Recrystallization of the product from methanol gave about 8 g of α-ethyl-β-(2,4,6-triiodo-3-aminophenyl-propionic acid, MP 147° to 150°C. The product could be further purified by precipitation of its morpholine salt from ether solution and regeneration of the free amino acid by treatment of a methanol solution of the morpholine salt with sulfur dioxide. The pure amino acid had the MP 155° to 156.5°C (corr).

A mixture of 57.1 g (0.1 mol) of α-ethyl-β-(3-amino-2,4,6-triiodophenyl)propionic acid, 250 ml of butyric anhydride and 1 ml of 70% perchloric acid was heated at 105°C for 5 hours. After cooling, the reaction mixture was poured onto ice, diluted to a volume of 3 liters with water, and heated on a steam bath with addition of solid sodium carbonate to keep the mixture basic. After all the excess butyric anhydride had been hydrolyzed, the mixture was made acid with dilute hydrochloric acid, the aqueous layer decanted from the resulting gummy solid, and the latter was then washed several times with water. The product was dissolved in acetic acid, decolorized with activated charcoal, and the solution while hot diluted with water to the point of turbidity. The product was collected by filtration and dried, giving 40 g of α-ethyl-β-(3-dibutyramido-2,4,6-triiodophenyl)propionic acid, MP 166° to 169.5°C (corr) when recrystallized from acetic acid. Reaction with sodium hydroxide gives the final product.

References

Merck Index 9636
I.N. p. 991
REM p. 1270
Archer, S. and Hoppe, J.O.; U.S. Patent 2,895,988; assigned to Sterling Drug, Inc.