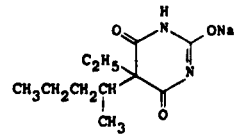
# PENTOBARBITAL SODIUM

**Therapeutic Function:** Hypnotic, sedative

**Chemical Name:** 5-Ethyl-5-(1-methylbutyl)-2,4,6-(1H,3H,5H)-pyrimidinetrione monosodium salt

**Common Name:** —

**Structural Formula:**



**Chemical Abstracts Registry No.:** 57-33-0; 76-74-4 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Nembutal | Abbott | U.S. | 1941 |
| Butylone | Hartz | Canada | — |
| Hypnol | Stickley | Canada | — |
| Mintal | Tanabe | Japan | — |
| Nebralin | Dorsey | U.S. | — |
| Neodrom | Minden | W. Germany | — |
| Novopentobarb | Novopharm | Canada | — |
| Penbon | Adams | Australia | — |
| Pentanca | Anca | Canada | — |
| Pentogen | Paul Maney | Canada | — |
| Pentone | Faulding | Australia | — |
| Prodormol | Teva | Israel | — |
| Repocal | Desitin | W. Germany | — |
| Sombutol | Farmus | Finland | — |
| Somnotol | M.T.C. | Canada | — |
| Sopental | Cont. Ethicals | S. Africa | — |

**Raw Materials**

di-n-Butyl ethyl 1-methyl-n-butylmalonate
Sodium
Butanol
Urea

**Manufacturing Process**

Sodium (9.6 parts) was dissolved in butanol (192 parts) and di-n-butyl ethyl 1-methyl-n-butylmalonate (62.8 parts) and urea (14.4 parts) were added to the warm solution with agitation. The mixture was then heated to reflux temperature in three quarters of an hour and maintained for 2 hours. The reaction mass was kept, water (150 parts) added, the aqueous portion separated, and the butanol layer extracted with water (3 x 50 parts). The combined aqueous extracts were then given 3 small extractions with benzene, the aqueous liquors separated, charcoaled, filtered and precipitated with concentrated hydrochloric acid (acid to congo-paper). The solid was collected, washed with water, dissolved in N-sodium hydroxide and reprecipitated with carbon dioxide. On recrystallization, from aqueous alcohol, the pentobarbitone was obtained.

**References**

Merck Index 6998
Kleeman & Engel p. 700

PDR pp. 531, 872, 1989
OCDS Vol. 1 p. 268 (1977)
I.N. p. 745
REM p. 1067
The Geigy Co. Ltd.; British Patent 650,354; February 21, 1951

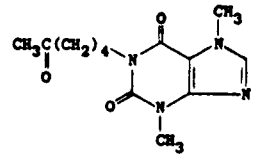
# PENTOXIFYLLINE

**Therapeutic Function:** Vasodilator

**Chemical Name:** 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione

**Common Name:** Oxpentifylline; vazofirin

**Structural Formula:**



**Chemical Abstracts Registry No.:** 6493-05-6

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Trental | Albert-Roussel | W. Germany | 1972 |
| Torental | Hoechst | France | 1974 |
| Trental | Hoechst | U.K. | 1975 |
| Trental | Albert-Farma | Italy | 1976 |
| Trental | Hoechst | Japan | 1977 |
| Agapurin | Spofa | Czechoslovakia | — |
| Techlon | Sawai | Japan | — |

**Raw Materials**

1-Bromo-5-hexanone
Theobromine sodium salt

**Manufacturing Process**

A solution of 35.4 g of 1-bromohexanone-5 in 200 ml of ethanol was gradually mixed at the reflux temperature with vigorous stirring with 39.7 g of theobromine-sodium in 100 ml of water. After 3 hours' reflux the unreacted theobromine was filtered off with suction, the filtrate was evaporated to dryness, the residue was dissolved in water and the solution was extracted with chloroform. The chloroform was distilled off and 1-(5'-oxohexyl)-3,7-dimethylxanthine was obtained as residue; after recrystallization from isopropanol, it melted at 102°C to 103°C (about 25% yield, calculated on the reacted theobromine).

**References**

Merck Index 7002
Kleeman & Engel p. 701
PDR p. 947
OCDS Vol. 2 p. 466 (1980)
I.N. p. 746
Mohler, W., Reiser, M. and Popendiker, K.; U.S. Patent 3,737,433; June 5, 1973; assigned to Chemische Werke Albert A.G. (W. Germany)

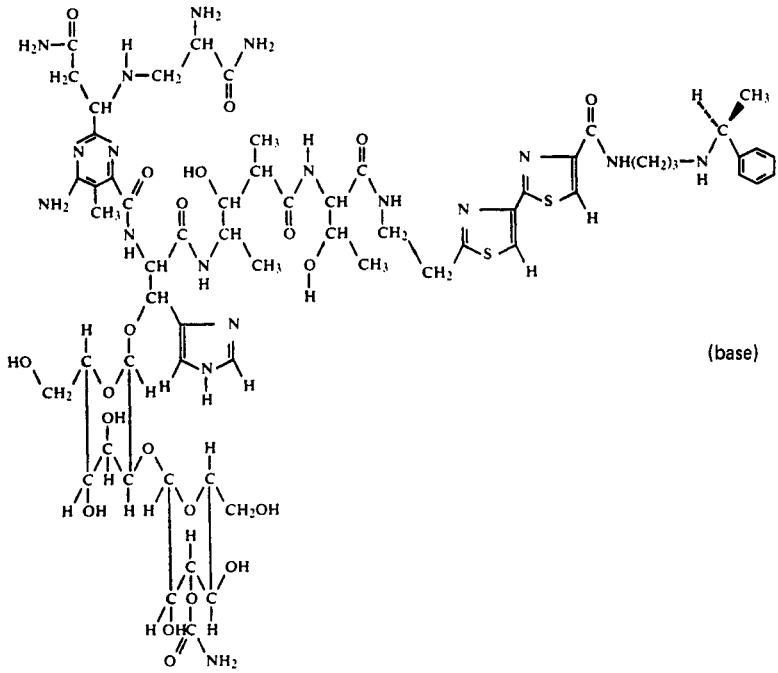
# PEPLOMYCIN SULFATE

**Therapeutic Function:** Antineoplastic

**Chemical Name:** 3-[(S)-1'-Phenylethylamino] propylaminobleomycin sulfate

**Common Name:** –

**Structural Formula:**



(base)

**Chemical Abstracts Registry No.:** 68247-85-8 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Pepleo | Nippon Kayaku | Japan | 1981 |

**Raw Materials**

Bleomycinic acid
N-[(S)-1'-Phenylethyl] -1,3-diaminopropane
Sulfuric acid

**Manufacturing Process**

In 400 ml of dimethylformamide was dissolved 15.0 g of bleomycinic acid (copper-containing form). To the solution kept at 0°C by cooling were added 1.1 ml of N-methylmorpholine and 10.3 g of 6-chloro-1-p-chlorobenzenesulfonyloxybenzotriazole (CCBT) as an activating compound. The mixture was stirred for 5 minutes at 0°C, then admixed with 5.3 g of N-[(S)-1'-phenylethyl] -1,3-diaminopropane and further stirred for 1 hour.

After termination of the reaction by adding 200 ml of a 25% aqueous acetic acid solution, the reaction mixture was mixed with 5 liters of cold acetone to precipitate the reaction product. The precipitate was collected by filtration, washed with acetone, and dissolved in 500 ml of distilled water. The resulting aqueous solution was immediately adjusted to pH 6.0 and poured into a column containing 2 liters of CM-Sephadex C-25 ($NH_4^+$ type) packed in 0.05 M aqueous ammonium chloride solution to adsorb bleomycins.

Using aqueous ammonium chloride solution, elution was performed by passing through the column 20 liters of eluent in which the concentration of ammonium chloride was continually increased from 0.05 to 1.0 M. The unreacted bleomycinic acid was found in the effluent at the ammonium chloride concentration of about 0.05 M and NK631 at the ammonium chloride concentration of about 0.45 M. Both fractions, which showed UV absorption at 292 mμ, were separately collected.

The NK631-containing fraction was poured into a resin column containing 2.6 liters of Amberlite XAD-2. The column was then washed thoroughly with water and eluted with 0.01 N hydrochloric acid in methanol-water (4:1 v/v). A total of 2.5 liters of the blue fraction, which showed UV absorption at 292 mμ, was collected. After evaporating off the methanol from the eluent fraction, the concentrate was adjusted to pH 6.0 with Dowex 44 ($OH^-$ type, an anion-exchange resin composed of a copolymer of epichlorohydrin and ammonia) and was freeze-dried to obtain 16.1 g (92% yield) of NK631 dihydrochloride (copper-containing form) in the form of blue amorphous powder.

By similar treatment, 280 mg of the unreacted bleomycinic acid (copper-containing form) were recovered.

In 200 ml of distilled water was dissolved 10.0 g of the NK631 dihydrochloride (copper-containing form). The solution was poured into a column containing 600 ml of Amberlite XAD-2 packed in distilled water. The column was washed successively with 2 liters of an aqueous solution containing 5% of EDTA-$Na_2$, 2.5 liters of a 5% aqueous sodium sulfate solution, and 630 ml of distilled water.

The column was then eluted with 0.0025 N sulfuric acid in methanol-water mixture (1:1 v/v). A total of 900 ml of fractions containing a substance which showed UV absorption at 290 mμ was collected. After removal of methanol by distillation, the residual liquid was adjusted to pH 6.0 with Dowex 44 ($OH^-$ type) and freeze-dried to obtain 9.3 g (95% yield) of NK631 monosulfate (copper-free form) in the form of pale yellowish-white amorphous powder.

**References**

Merck Index 7011
DFU 6 (2) 101 (1981)
DOT 17 (8) 331 (1981)
Takita, T., Fujii, A., Fukuoka, T., Muraoka, Y., Yoshioka, O. and Umezawa, H.; U.S. Patent 4,195,018; March 25, 1980; assigned to Nippon Kayaku K.K.
Umezawa, H., Maeda, K., Takita, T., Nakayama, Y., Fujii, A. and Shimada, N.; U.S. Patent 3,846,400; November 5, 1974; assigned to Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai.

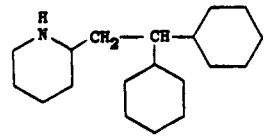
## PERHEXILINE MALEATE

**Therapeutic Function:** Coronary vasodilator

**Chemical Name:** 2-(2,2-dicyclohexylethyl)piperidine maleate

**Common Name:** —

Structural Formula:



(base)

**Chemical Abstracts Registry No.:** 6724-53-4; 6621-47-2 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Pexid | Merrell-Tourade | France | 1973 |
| Pexid | Merrell | W. Germany | 1974 |
| Pexid | Merrell | Italy | 1974 |
| Pexid | Merrell | U.K. | 1975 |
| Corzepin | Prodes | Spain | — |
| Daprin | Gerardo Ramon | Argentina | — |

**Raw Materials**

Ethyl formate
α-Picoline
Sodium hydroxide
Maleic acid
Cyclohexylmagnesium bromide
Hydrogen chloride
Hydrogen

**Manufacturing Process**

1,1-Dicyclohexyl-2-(2'-pyridyl)ethanol hydrochloride (5 grams) was dehydrated by heating with 25 ml of concentrated hydrochloric acid at steam bath temperature for 10 minutes. 70 ml of water were added to the reaction mixture to give the crystalline hydrochloride salt. The product, 1,1-dicyclohexyl-2-(2'-pyridyl)ethylene hydrochloride, was recrystallized from methanol-ethyl acetate to yield a white solid melting at 150°-151.5°C.

1,1-Dicyclohexyl-2-(2'-pyridyl)ethylene hydrochloride (15 grams) in 150 ml of ethanol was hydrogenated in the presence of platinum oxide at about 60 pounds per square inch of hydrogen pressure. The product, 1,1-dicyclohexyl-2-(2'-piperidyl)ethane hydrochloride, crystallized from a mixture of methanol and methyl ethyl ketone as a white solid melting at 243° to 245.5°C.

The hydrochloride salt was neutralized with 10% sodium hydroxide solution and the free base so produced was dissolved in ether. The ether solution was dried over anhydrous magnesium sulfate. Addition of an excess of maleic acid in methanol to the solution yielded the acid maleate salt which melted at 188.5°-191°C.

The starting material was obtained by reacting ethyl formate with cyclohexylmagnesium bromide to give dicyclohexylcarbinol. That is oxidized to dicyclohexylketone and then reacted with α-picoline.

**References**

Merck Index 7026
Kleeman & Engel p. 703
DOT 10 (8) 299 (1974)
I.N. p. 747
REM p. 854
Richardson-Merrell Inc.; British Patent 1,025,578; April 14, 1966
Horgan, S.W., Palopoli, F.P. and Schwoegler, E.J.; U.S. Patent 4,069,222; January 17, 1978; assigned to Richardson-Merrell Inc.

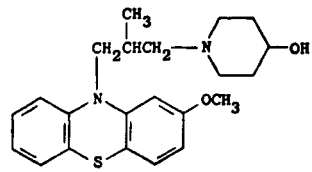
# PERIMETHAZINE

**Therapeutic Function:** Tranquilizer

**Chemical Name:** 1-[3-(2-methoxyphenothiazin-10-yl)-2-methylpropyl]-4-piperidinol

**Common Name:** —

**Structural Formula:**



**Chemical Abstracts Registry No.:** 13093-88-4

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Leptryl | Roger Bellon | France | 1970 |

**Raw Materials**

3-Methoxy-10-(3-chloro-2-methylpropyl)phenthiazine
4-Hydroxypiperidine

**Manufacturing Process**

A solution of 3-methoxy-10-(3-chloro-2-methylpropyl)phenthiazine (9.65 grams) and 4-hydroxypiperidine (6.1 grams) in xylene (10cc) is heated under reflux for 5 hours. After cooling the mixture is diluted with ether (60 cc) and the basic compounds are extracted by agitation with water (30 cc) and 4 N hydrochloric acid (20 cc). The aqueous acid phase is made alkaline with 4 N sodium hydroxide solution (23 cc) and the liberated base is extracted with ether. The ethereal solution is washed with water (60 cc) and dried over sodium sulfate. Finally the solvent is distilled off on a water-bath.

The solid residue obtained is recrystallized from a mixture (15:85) of benzene and cyclohexane and there is obtained 3-methoxy-10-[2-methyl-3-(4-hydroxy-1-piperidyl)-propyl]-phenthiazine (5.7 grams) as a white crystalline powder, MP 137°-138°C.

**References**

Merck Index 7030
Kleeman & Engel p. 704
DOT 6 (4) 190 (1970)
I.N. p. 748
Jacob, R.M. and Robert, J.G.; U.S. Patent 3,075,976; January 29, 1963; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

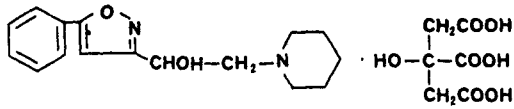
# PERISOXAL CITRATE

**Therapeutic Function:** Antiinflammatory, analgesic

**Chemical Name:** 3-(2-Piperidino-1-hydroxyethyl)-5-phenylisoxazole citrate

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 2055-44-9 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Isoxal | Shionogi | Japan | 1979 |

**Raw Materials**

3-(2-Methylthio-2-piperidinoacetyl)-5-phenylisoxazole
Sodium borohydride
Citric acid

**Manufacturing Process**

Crude crystals of 3-(2-methylthio-2-piperidinoacetyl)-5-phenylisoxazole (1.631 g) are suspended in 20 ml of methanol without being further purified and the suspension is stirred after a portionwise addition (in about 10 minutes) of 143 mg (3.78 mmol) of sodium borohydride at room temperature for about 30 minutes.

The methanol in the reaction mixture (pale yellow solution) is then removed by evaporation under reduced pressure to leave a residue which is subsequently dissolved in 30 ml of benzene. The benzene solution is shaken four times with 20 ml of 4N hydrochloric acid each time to extract the basic substance. Each of the hydrochloric acid layers is washed once with 20 ml of benzene and combined together to be neutralized with potassium carbonate while being ice-cooled until it becomes basic (pH = 10).

The liberated crystalline substance is extracted twice with 50 ml of dichloromethane each time. After being separated, the dichloromethane layers are combined and washed once with 30 ml of water and dried over sodium sulfate. The solvent of the layer is removed by evaporation under reduced pressure to leave a crystalline residue (72.56 mg, 53% crude yield).

Recrystallization of this product from dichloromethane-ether (1:4) affords needles of 3-(2-piperidino-1-hydroxyethyl)-5-phenylisoxazole (701 mg, 51.3% as an overall yield calculated based on the starting material, melting point 104°C to 106°C. The product thus obtained may be reacted with citric acid to give the citrate.

**References**

Merck Index 7038
DFU 4 (4) 269 (1979)
I.N. p. 748
Hirai, S. and Kawata, K.; U.S. Patent 3,939,167; February 17, 1976; assigned to Shionogi & Co., Ltd.

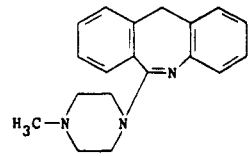
# PERLAPINE

**Therapeutic Function:** Hypnotic

**Chemical Name:** 6-(4-methyl-1-piperazinyl)-11H-dibenz[b,e]azepine

**Common Name:** 6-(4-methyl-1-piperazinyl)morphanthridine

**Structural Formula:**



**Chemical Abstracts Registry No.:** 1977-11-3

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Hypnodin | Takeda | Japan | 1974 |
| Pipnodine | Takeda | Japan | – |

**Raw Materials**

o-Aminodiphenylmethane
Aluminum chloride
N-Methylpiperazine
Phosgene
Phosphorus oxychloride

**Manufacturing Process**

The 5,6-dihydro-6-oxo-morphanthridine used as a starting material is usefully obtained in the following way. 30.2 grams of o-aminodiphenylmethane are dissolved in 65 ml of absolute toluene and, while stirring and at a temperature of between 0° and -10°C, 140 ml of 20% phosgene solution in toluene are added drop by drop. By bubbling phosgene slowly through it the milky mixture is heated within 30 minutes to reflux temperature, which is maintained during some 20 minutes. While stirring vigorously, dry nitrogen is passed into the boiling reaction mixture for 10 minutes. After evaporation of the solvent there are obtained by vacuum distillation 29.7 grams (86% of the theory of o-isocyanatodiphenylmethane of boiling point 169°C/12 mm Hg.

21.1 grams of aluminum chloride are heated in 110 ml of o-dichlorobenzene to 80°C and, while stirring, a solution of 29.7 grams of o-isocyanatodiphenylmethane in 60 ml of o-dichlorobenzene is added drop by drop, whereupon the temperature of the mixture rises to 120°C. This temperature is maintained for one hour while stirring. After cooling the reaction mixture is poured into 200 ml of 2 N hydrochloric acid, whereupon a brown precipitate is formed. After steam distillation the residue is isolated by filtration and crystallized from acetone/water. There are obtained 28.6 grams (97% of the theory) of 5,6-dihydro-6-oxo-morphanthridine of melting point 201°-203°C.

A mixture of 4.9 grams of 5,6-dihydro-6-oxo-morphanthridine, 37 ml of phosphorus oxychloride and 1.5 ml of dimethylaniline is heated for 3 hours at reflux. The viscous oil, obtained by evaporation of the reaction mixture in vacuo at 60°C, is diluted with 20 ml of absolute dioxane and, after adding 30 ml of N-methylpiperazine, heated for 4 hours at reflux. The resulting clear solution is evaporated in vacuo at 60°C to dryness. The residue is distributed between ether and ammonia water. The ethereal solution is separated, washed with water and then extracted with 1 N acetic acid. The acetic acid extract is mixed with ammonia water and then extracted with ether. The ethereal solution is washed with water, dried over sodium sulfate, filtered through alumina and evaporated.

The residue is caused to crystallize from ether/petroleum ether, and recrystallized from acetone/petroleum ether. 6.0 grams (88% of the theory) of 6-(4-methyl-1-piperazinyl)-morphanthridine of melting point 138°-138.5°C are obtained.

**References**

Merck Index 7040
Kleeman & Engel p. 705
OCDS Vol. 2 p. 425 (1980)
DOT 11 (2) 76 (1975)
I.N. p. 748
Schmutz, J., Hunziker, F. and Kunzle, F.M.; U.S. Patent 3,389,139; June 18, 1968; assigned to Dr. A. Wander, SA, Switzerland

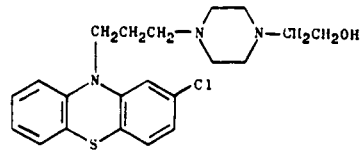
# PERPHENAZINE

**Therapeutic Function:** Tranquilizer

**Chemical Name:** 4-[3-(2-chlorophenothiazin-10-yl)propyl]-1-piperazineethanol

**Common Name:** Chlorpiprazine

**Structural Formula:**




**Chemical Abstracts Registry No.:** 58-39-9

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Trilafon | Schering | U.S. | 1957 |
| Decentan | Merck | W. Germany | – |
| Etrafon | Schering | U.S. | – |
| Fentazin | Allen & Hanburys | U.K. | – |
| F-Mon | Nippon Shinyaku | Japan | – |
| Peratsin | Farmos | Finland | – |
| Perfenil | Scalari | Italy | – |
| Perphenan | Taro | Israel | – |
| Phenazine | I.C.N. | Canada | – |
| Triavil | MSD | U.S. | – |
| Trilifan | Cetrane | France | – |
| Triomin | Yamanouchi | Japan | – |

**Raw Materials**

2-Chlorophenothiazine
Piperazine
1-Bromo-3-chloropropane
2-Bromoethanol

**Manufacturing Process**

A mixture of 155 parts of 2-chloro-10-(γ-chloropropyl)phenothiazine, 76 parts of sodium iodide, 216 parts of piperazine and 2,000 parts of butanone is refluxed for 8 hours, con-

centrated and extracted with dilute hydrochloric acid. The extract is rendered alkaline by addition of dilute potassium carbonate and benzene or chloroform extracted. This extract is washed with water, dried over anhydrous potassium carbonate, filtered and evaporated. Vacuum distillation at 0.1 mm pressure yields 2-chloro-10-[γ-(N-piperazino)propyl] phenothiazine at about 214°-218°C.

A stirred mixture of 5 parts of 2-chloro-10-[γ-(N-piperazino)propyl] phenothiazine, 1.92 parts of 2-bromoethanol, 2.11 parts of potassium carbonate and 35 parts of toluene is refluxed for 5 hours. The mixture is treated with water and benzene and the organic layer is separated, washed with water, dried over anhydrous potassium carbonate, filtered and evaporated. The residue is distilled at about 240°-244°C and 0.15 mm pressure to yield 2-chloro-10-[γ-(N'-β-hydroxyethyl-N-piperazino)-propyl] phenothiazine according to U.S. Patent 2,838,507.

The 2-chloro-10-(γ-chloropropyl)phenothiazine starting material is produced from 2-chlorophenothiazine and 1-bromo-3-chloropropane.

**References**

Merck Index 7044
Kleeman & Engel p. 705
PDR pp. 1217, 1617, 1655
OCDS Vol. 1 p. 383 (1977)
DOT 9 (6) 228 (1973)
I.N. p. 749
REM p. 1090

Cusie, J.W. and Hamilton, R.W.; U.S. Patent 2,838,507; June 10, 1958; assigned to G.D. Searle & Co.

Sherlock, M.H. and Sperber, N.; U.S. Patent 2,860,138; November 11, 1958; assigned to Schering Corporation

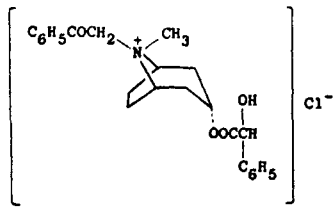
## PHENACTROPINIUM CHLORIDE

**Therapeutic Function:** Antihypertensive

**Chemical Name:** α-Hydroxybenzeneacetic acid 8-methyl-8-[(2-oxo-2-phenyl)-ethyl]-8-azoniabicyclo[3.2.1]oct-3-yl ester chloride

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** –

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Trophenium | Amer. Cyanamid | U.S. | 1961 |
| Trophenium | Duncan Flockhart | U.K. | – |

**Raw Materials**

Homatropine
Phenacyl chloride

**Manufacturing Process**

330 g (1.2 M) of homatropine were dissolved in 1 liter of dry methyl ethyl ketone and gently refluxed on a water-bath during the gradual addition of a solution of 204 g (1.32 M) redistilled phenacyl chloride in 200 ml of the same solvent. After 10 to 15 minutes 1 g of previously prepared homatropine phenacyl chloride was added to avoid formation of a supersaturated solution of the quaternary compound. Reflux was continued for 9 hours, then the thick suspension was allowed to cool, filtered and washed with 200 ml methyl ethyl ketone to yield 490 g (95%) slightly creamy solid, MP 188°C to 191°C.

For purification the crude quaternary salt was dissolved in hot ethyl alcohol (2 ml/g) and warm dry acetone (8 ml/g) was stirred into the clear filtrate. On cooling, 387 g (78% recovery) of a pure white powder, MP 195°C to 197°C, were obtained, in which the ionizable chlorine assayed at 99.7% of the theoretical value.

**References**

Merck Index 7067
I.N. p. 752
Johnston, R.G. and Spencer, K.E.V.; U.S. Patent 2,828,312; March 25, 1958; assigned to T. & H. Smith, Ltd. (U.K.)

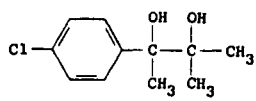
# PHENAGLYCODOL

**Therapeutic Function:** Tranquilizer

**Chemical Name:** 2-(4-Chlorophenyl)-3-methyl-2,3-butanediol

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 79-93-6

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Ultran | Lilly | U.S. | 1957 |
| Felixyn | Radiumpharma | Italy | – |

**Raw Materials**

p-Chloroacetophenone
Hydrogen chloride
Ethanol
Magnesium
Sodium cyanide
Sodium hydroxide
Methyl iodide

**Manufacturing Process**

To a mixture of 460 g of p-chloroacetophenone, 350 ml of ether and 500 ml of water are added 410 g of sodium cyanide, with vigorous stirring. The reaction mixture is cooled to about 5°C to 10°C and 700 ml of concentrated hydrochloric acid are added at such a rate that no hydrogen cyanide is formed and the temperature of the mixture does not rise above 10°C. After the addition of the acid is complete, the reaction mixture is stirred for about three hours at room temperature, and allowed to separate into an aqueous and an organic phase. The organic phase is removed from the aqueous phase, and the aqueous phase and any salt which may have separated in the course of the reaction are washed with about 300 ml of ether. The combined ether washings and organic phase are dried over anhydrous magnesium sulfate, and the ether is removed by evaporation in vacuo at room temperature. The residue is poured with stirring into 800 ml of concentrated hydrochloric acid kept at about 0°C by cooling with solid carbon dioxide. The acid mixture is saturated with gaseous hydrogen chloride at 0°C, and stirred at room temperature overnight. The resulting precipitate of p-chloroatrolactamide is removed by filtration, washed by slurrying with water and dried. After recrystallization from ethanol, p-chloroatrolactamide melts at about 105°C to 107°C.

A mixture of 200 g of p-chloroatrolactamide and 1 liter of 25% sodium hydroxide solution is refluxed with stirring for about sixteen hours. The reaction mixture is then poured over cracked ice and diluted with water to a volume of about 3 liters. The aqueous solution is washed with two 1 liter portions of ether, and acidified with concentrated hydrochloric acid, whereupon a precipitate of p-chloroatrolactic acid forms. The precipitated acid is removed by filtration, and is dissolved in 500 ml of ether, washed with two 250 ml portions of water and dried. The ether is removed by evaporation. p-chloroatrolactic acid thus prepared melts at about 117°C to 120°C.

A mixture of 185 g of p-chloroatrolactic acid, 600 ml of ethanol and 60 ml of concentrated sulfuric acid is refluxed for about twelve hours. About half the solvent is then removed by evaporation in vacuo at room temperature, the residue is poured over cracked ice, and diluted with water to a volume of about 2 liters. The ethyl p-chloroatrolactate formed in the reaction is extracted with two 1 liter portions of ether. The combined ether extracts are washed with successive 200 ml portions of water, 5% sodium carbonate solution, and water, and are dried over anhydrous magnesium sulfate. The dried ether solution is subjected to fractional distillation, and the fraction boiling at about 90°C to 100°C at a pressure of 0.1 mm of mercury, is collected. The distillate consists of ethyl p-chloroatrolactate.

To a solution of 2 mols of methylmagnesium iodide in 1.5 liters of ether are added with vigorous stirring 107 g (0.5 mol) of ethyl p-chloroatrolactate. The reaction mixture is stirred for about sixteen hours, and is then decomposed by the addition of about 320 ml of saturated aqueous ammonium chloride solution. After standing, the ether layer is decanted from the mixture and the aqueous phase and the precipitated salts are washed with several 500 ml portions of ether. The combined ether solution and washings are washed with successive 500 ml portions of 5% ammonium chloride solution and water, are dried over anhydrous magnesium sulfate, and are evaporated to dryness in vacuo. The crystalline residue consisting of 2-p-chlorophenyl-3-methyl-2,3-butanediol, is recrystallized from a mixture of benzene and petroleum ether.

2-p-chlorophenyl-3-methyl-2,3-butanediol thus prepared melts at about 66°C to 67°C.

**References**

Merck Index 7070
Kleeman & Engel p. 709
OCDS Vol. 1 p. 219 (1977)
I.N. p. 752
Mills, J.; U.S. Patent 2,812,363; November 5, 1957; assigned to Eli Lilly & Co.

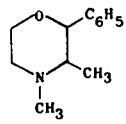
# PHENDIMETRAZINE TARTRATE

**Therapeutic Function:** Antiobesity

**Chemical Name:** 3,4-dimethyl-2-phenylmorpholine bitartrate

**Common Name:** 3,4-dimethyl-2-phenyltetrahydro-1,4-oxazine bitartrate

**Structural Formula:**




(base)

**Chemical Abstracts Registry No.:** 50-58-8; 634-03-7 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Plegine | Ayerst | U.S. | 1961 |
| Statobex | Lemmon | U.S. | 1972 |
| Bacarate | Tutag | U.S. | 1972 |
| Prelu-2 | Boehr. Ingel. | U.S. | 1980 |
| Sprx 105 | Tutag | U.S. | 1980 |
| Obezine | Western Research | U.S. | 1981 |
| X-Trozine | Rexar | U.S. | 1981 |
| Hyrex-105 | Hyrex | U.S. | 1983 |
| Adipost | Ascher | U.S. | 1983 |
| Slyn-LL | Edwards | U.S. | 1983 |
| Trimcaps | Mayrand | U.S. | 1983 |
| Adipo II | Sig | U.S. | – |
| Adphen | Ferndale | U.S. | – |
| Amphasub | Palmedico | U.S. | – |
| Anoxine T | Winston Pharm. | U.S. | – |
| Arcotrol | Arco | U.S. | – |
| Bacarate | Reid Provident | U.S. | – |
| Bontril | Carnrick | U.S. | – |
| Di-Ap-Trol | Foy | U.S. | – |
| Dyrexan | Trimen | U.S. | – |
| Ephemet | Canright | U.S. | – |
| Fringanor | Sobio | France | – |
| Melfiat | Reid-Rowell | U.S. | – |
| Neo-Nilorex | A.V.P. | U.S. | – |
| Obe-Del | Marlop | U.S. | – |
| Obepar | Parmed | U.S. | – |
| Obesan | SCS Pharmalab | S. Africa | – |
| Obex-LA | Rio Ethicals | S. Africa | – |
| Pan-Rexin | Pan American | U.S. | – |
| Phenazine | Jenkins | U.S. | – |
| Reducto | Arcum | U.S. | – |
| Reton | Tri-State | U.S. | – |
| Stodex | Jalco | U.S. | – |
| Symetra | Westerfield | U.S. | – |
| Trimstat | Laser | U.S. | – |
| Wehless | Hauck | U.S. | – |
| Weightrol | N. Amer. Pharm. | U.S. | – |
| X-Trozine | Rexar | U.S. | – |

**Raw Materials**

Propiophenone
2-Methylaminomethanol
Bromine
Formic acid

**Manufacturing Process**

A mixture of 61 grams 1-phenyl-1-oxo-2-(N-methyl-N-ethanolamino)-propane hydrochloride and 100 cc 98-100% formic acid was refluxed at the boiling point at atmospheric pressure for 45 minutes on an oil bath. Thereafter, the oil bath temperature was increased to 180°C and as much of the excess unreacted formic acid as possible was distilled off. A vigorous evolution of carbon dioxide developed during the distillation, which ceased after approximately 45 additional minutes. The honey-yellow syrup which remained as the distillation residue was worked up by admixing it with about six volumes of water and adjusting the aqueous mixture to alkaline reaction with concentrated sodium hydroxide. An oily phase separated out which was extracted with ether. The ether extract was washed with water and dried over potassium carbonate. The solvent was distilled off and the distillation residue was fractionally distilled in vacuo. The base boils at 132°-133°C at 12 mm. The yield was 93% of theory. Reaction with tartaric acid gave the final product.

The starting material is produced by reacting propiophenone with bromine and then reacting the α-bromopropiophenone produced with 2-methylaminomethanol.

**References**

Merck Index 7088
Kleeman & Engel p. 711
PDR pp. 633, 679, 778, 928, 948, 992, 1448, 1450, 1807
OCDS Vol. 1 p. 260 (1977) & 2, 261 (1980)
I.N. p. 754
REM p. 892
Heel, W. and Zeile, K.; U.S. Patent 2,997,469; August 22, 1961; assigned to C.H. Boehringer Sohn, Germany

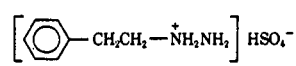
## PHENELZINE SULFATE

**Therapeutic Function:** Psychostimulant

**Chemical Name:** (2-phenethyl)hydrazine sulfate

**Common Name:** —

**Structural Formula:**



**Chemical Abstracts Registry No.:** 156-51-4; 51-71-8 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Nardil | Parke Davis | U.S. | 1959 |
| Nardelzine | Substantia | France | — |

**Raw Materials**

Phenethylbromide
Hydrazine hydrate

**Manufacturing Process**

To a refluxing solution containing 147.5 grams of 85% hydrazine hydrate in 500 cc of ethanol was added, during a period of 5 hours, 92.5 grams of phenethylbromide (0.50 mol) in 150 cc of ethanol. Stirring and refluxing were continued for two hours. The ethanol was removed by distillation and the residue extracted repeatedly with ether. The ether was dried with potassium carbonate and the product base collected by distillation, BP 74°C/0.1 mm, yield 52.3 grams (77%). The base is reacted with sulfuric acid in propanol to give the sulfate.

**References**

Merck Index 7089
Kleeman & Engel p. 711
PDR p. 1368
OCDS Vol. 1 p. 74 (1977)
I.N. p. 754
REM p. 1096

Biel, J.H.; U.S. Patent 3,000,903; September 19, 1961; assigned to Lakeside Laboratories, Inc.

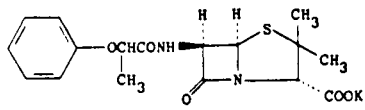
# PHENETHICILLIN POTASSIUM

**Therapeutic Function:** Antibacterial

**Chemical Name:** 3,3-Dimethyl-7-oxo-6-[(1-oxo-2-phenoxypropyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid potassium salt

**Common Name:** Penicillin MY

**Structural Formula:**




**Chemical Abstracts Registry No.:** 132-93-4; 147-55-7 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Syncillin | Bristol | U.S. | 1959 |
| Ro-Cillin | Rowell | U.S. | 1960 |
| Chemiphen | Squibb | U.S. | 1960 |
| Semopen | Massengill | U.S. | 1960 |
| Dramcillin-S | White | U.S. | 1960 |
| Maxipen | Roerig | U.S. | 1960 |
| Darcil | Wyeth | U.S. | 1960 |
| Alpen | Schering | U.S. | 1960 |
| Altocillin | Caber | Italy | — |
| Bendralan | Antibioticos | Spain | — |
| Broxil | Beecham | U.K. | — |
| Metilpen | Boniscontro-Gazzone | Italy | — |
| Optipen | C.S.L. | Australia | — |
| Pen-200 | Pfizer | W. Germany | — |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Peniplus | Fumouze | France | – |
| Penopen | Pliva | Yugoslavia | – |
| Penorale | Lusofarmaco | Italy | – |
| Synthecilline | Bristol | France | – |
| Synthepen | Meiji | Japan | – |

**Raw Materials**

α-Phenoxypropionic acid
6-Aminopenicillanic acid
Isobutyl chloroformate
Potassium 2-ethylhexanoate

**Manufacturing Process**

Triethylamine (1.5 ml) was added to a cold solution (10°C) of α-phenoxypropionic acid (1.66 g, 0.01 mol) in 15 ml of pure dioxane, with stirring and cooling to 5°C to 10°C while isobutyl chloroformate (1.36 g, 0.01 mol) in 5 ml of dioxane was added dropwise. Then the mixture was stirred for ten minutes at 5°C to 8°C. A solution of 6-amino-penicillanic acid (2.16 g, 0.01 mol) in 15 ml of water and 2 ml of triethylamine was then added dropwise while the temperature was maintained below 10°C. The resulting mixture was stirred in the cold for 15 minutes then at room temperature for 30 minutes, diluted with 30 ml of cold water and extracted with ether which was discarded. The cold aqueous solution was then covered with 75 ml of ether and acidified to pH 2 with 5 N $H_2SO_4$. After shaking, the ether layer containing the product 6-(α-phenoxypropionamido)penicillanic acid, was dried for ten minutes over anhydrous sodium sulfate and filtered. Addition of 6 ml of dry n-butanol containing 0.373 g/ml of potassium 2-ethylhexanoate precipitated the potassium salt of the product as a colorless oil which crystallized on stirring and scratching and was collected, dried in vacuo and found to weigh 2.75 g, to melt at 217°C to 219°C.

**References**

Merck Index 7093
Kleeman & Engel p. 712
OCDS Vol. 1 p. 410 (1977)
I.N. p. 755
Beecham Research Laboratories, Ltd.; British Patent 877,120; September 13, 1961

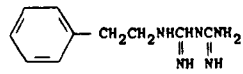
## PHENFORMIN

**Therapeutic Function:** Antidiabetic

**Chemical Name:** N-(2-Phenylethyl)imidodicarbonimidic diamide

**Common Name:** Phenethyldiguanide

**Structural Formula:**



**Chemical Abstracts Registry No.:** 114-86-3

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| DBI | Geigy | U.S. | 1959 |
| Meltrol | U.S.V. Pharm | U.S. | 1971 |
| Adiabetin | Arcana | Austria | – |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Antipond | Arcana | Austria | – |
| Cronoformin | Guidotti | Italy | – |
| De Be J | Isa | Brazil | – |
| Debeone | U.S.V. | U.S. | – |
| Diabis | Funk | Spain | – |
| Dibein | Pharmacia | Sweden | – |
| Dibophen | Polfa | Poland | – |
| Insoral | U.S.V. | U.S. | – |
| Kataglicina | Marxer | Italy | – |
| Prontoformin | Guidotti | Italy | – |

**Raw Materials**

β-Phenylethylamine
Hydrogen chloride
Dicyandiamide

**Manufacturing Process**

15.76 g of β-phenylethylamine hydrochloride and 8.4 g of dicyandiamide were ground and intimately mixed. The mixture was heated in an oil bath in a 3-neck flask fitted with a thermometer and stirrer, and the mixture began to melt at a bath temperature of 125°C and was completely fluid at 130°C. Further heating at 145°C to 150°C initiated an exothermic reaction and the temperature of the fusion mixture (156°C) exceeded the oil bath temperature (150°C) by 6°. Heating was continued for one hour at bath temperature of 148°C to 150°C. The reaction mixture was cooled, dissolved in about 100 cc of methanol and filtered. The methanol filtrate was concentrated under reduced pressure, cooled and the product (β-phenylethylbiguanide hydrochloride) filtered off and recrystallized from 95% isopropanol.

**References**

Merck Index 7099
OCDS Vol. 1 p. 75 (1977)
I.N. p. 755
Shapiro, S.L. and Freedman, L.; U.S. Patent 2,961,377; November 22, 1960; assigned to U.S. Vitamin & Pharmaceutical Corp.

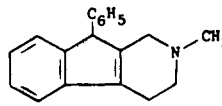
## PHENINDAMINE TARTRATE

**Therapeutic Function:** Antihistaminic

**Chemical Name:** 2,3,4,9-tetrahydro-2-methyl-9-phenyl-1H-indeno[2,1,c]pyridine tartrate

**Common Name:** 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene tartrate

**Structural Formula:**



(base)

**Chemical Abstracts Registry No.:** 569-59-5; 82-88-2 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Thephorin | Roche | U.S. | 1947 |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Nolahist | Carnrick | U.S. | 1982 |
| Nolamine | Carnrick | U.S. | – |
| Pernovin | Chinoin | Hungary | – |
| PV-Tussin | Reid-Rowell | U.S. | – |

**Raw Materials**

Acetophenone
Formaldehyde
Hydrogen bromide
Potassium thiocyanate
Methylamine
Sodium hydroxide
Hydrogen

**Manufacturing Process**

A mixture of 750 grams of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine and 2,500 cc of 48% hydrobromic acid is refluxed for about 20 minutes. It is then poured into 8 liters of water. An oily precipitate appears which on standing crystallizes. It is filtered and crystallized from about 3.5 liters of alcohol. 2-Methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, MP 201°-203°C, is obtained.

A mixture of 680 grams of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, 6,000 cc of water and about 100 grams of Raney-nickel catalyst is hydrogenated at room temperature and at about 1,000 lb pressure for a period of three hours. The catalyst is filtered. The clear filtrate is treated with a solution of 240 grams potassium thiocyanate in 400 cc of water. A heavy solid precipitates from which the supernatant liquid is decanted.

The residue is dissolved in 10 liters of boiling alcohol with stirring in the presence of nitrogen. The solution is cooled to room temperature under nitrogen, and then allowed to stand overnight. 2-Methyl-9-phenyl-tetrahydro-1-pyridindene thiocyanate separates in crystals of MP 188°-189°C. From the concentrated filtrate an additional amount is obtained. The corresponding free base, prepared by treating the slightly soluble thiocyanate in aqueous suspension with sodium hydroxide and extracting with ether, has a MP of 90°-91°C. It forms a tartrate of MP 160°C.

The starting material was prepared by reacting acetophenone, methylamine and formaldehyde followed by treatment of the intermediate with sodium hydroxide.

**References**

Merck Index 7103
Kleeman & Engel p. 713
PDR pp. 781, 1448
I.N. p. 756
Plati, J.T. and Wenner, W.; U.S. Patent 2,470,108; May 17, 1949; assigned to Hoffmann-La Roche Inc.

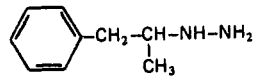
## PHENIPRAZINE

**Therapeutic Function:** Antihypertensive

**Chemical Name:** (1-Methyl-2-phenylethyl)hydrazine

**Common Name:** –

**Structural Formula:**



**Chemical Abstracts Registry No.:** 55-52-7

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Catron | Lakeside | U.S. | 1959 |
| Catroniazide | Lakeside | U.S. | – |

**Raw Materials**

1-Phenyl-2-propylidenylhydrazine
Acetic acid
Hydrogen

**Manufacturing Process**

A solution containing 741 g (5.0 mols) of 1-phenyl-2-propylidenylhydrazine, 300 g (5.0 mols) of glacial acetic acid and 900 cc of absolute ethanol was subjected to hydrogenation at 1,875 psi of hydrogen in the presence of 10 g of platinum oxide catalyst and at a temperature of 30°C to 50°C (variation due to exothermic reaction). The catalyst was removed by filtration and the solvent and acetic acid were distilled. The residue was taken up in water and made strongly alkaline by the addition of solid potassium hydroxide. The alkaline mixture was extracted with ether and the ether extracts dried with potassium carbonate. The product was collected by fractional distillation, BP 85°C (0.30 mm); yield 512 g (68%).

The hydrochloride salt was formed in a mixture of 1:10 isopropyl alcohol:diisopropyl ether and recrystallized from acetonitrile, yield 87%, MP 124°C to 125°C.

**References**

Merck Index 7105
OCDS Vol. 1 p. 74 (1977)
I.N. p. 757
Biel, J.H.; U.S. Patent 2,978,461; April 4, 1961; assigned to Lakeside Laboratories, Inc.

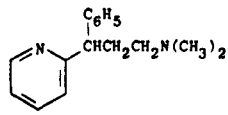
# PHENIRAMINE MALEATE

**Therapeutic Function:** Antihistaminic

**Chemical Name:** N,N-dimethyl-γ-phenyl-2-pyridine-propanamine maleate

**Common Name:** Prophenpyridine

**Structural Formula:**



(base)

**Chemical Abstracts Registry No.:** 132-20-7; 86-21-5 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Trimeton Maleate | Schering | U.S. | 1948 |
| Avil | Albert-Roussel | W. Germany | – |
| Citra Forte | Doyle | U.S. | – |
| Daneral | Hoechst | U.K. | – |
| Dristan | Whitehall | U.S. | – |
| Fenamine | Fawns & McAllan | Australia | – |
| Fiogesic | Sandoz | U.S. | – |
| Inhiston | Upjohn | U.S. | – |
| Poly-Histine | Bock | U.S. | – |
| Ru-Tuss | Boots | U.S. | – |
| S.T. Forte | Scot-Tussin | U.S. | – |
| Triaminic | Dorsey | U.S. | – |
| Tussirex | Scot-Tussin | U.S. | – |

**Raw Materials**

2-Benzylpyridine
β-Dimethylaminoethyl chloride
Potassium amide
Maleic acid

**Manufacturing Process**

According to U.S. Patent 2,676,964: to 1.0 mol of potassium amide in 3 liters of liquid ammonia, is added 1.0 mol of 2-benzylpyridine. After 15 minutes, 1.1 mols of β-dimethylaminoethyl chloride are added. The ammonia is allowed to evaporate and the reaction product decomposed with water and ether extracted. The ether layer is dried over sodium sulfate and after evaporation the residue is distilled, giving the 3-phenyl-3-(2-pyridyl)-N,N-dimethylpropylamine, BP 139°-142°C/1-2 mm. The maleate is produced by reaction with maleic acid.

**References**

Merck Index 7106
Kleeman & Engel p. 713
PDR pp. 674, 688, 692, 849, 1583, 1662, 1899
OCDS Vol. 1 p. 77 (1977)
I.N. p. 757
REM p. 1131
Sperber, N., Papa, D. and Schwenk, E.; U.S. Patent 2,567,245; September 11, 1951; assigned to Schering Corporation
Sperber, N., Papa, D. and Schwenk, E.; U.S. Patent 2,676,964; April 27, 1954; assigned to Schering Corporation

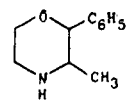
## PHENMETRAZINE

**Therapeutic Function:** Antiobesity drug

**Chemical Name:** 3-methyl-2-phenylmorpholine

**Common Name:** Oxazimedrine

**Structural Formula:**



**Chemical Abstracts Registry No.:** 134-49-6; 1707-14-8 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Preludin | Boehr. Ingel. | U.S. | 1956 |
| Anorex | Pfizer | U.S. | — |
| Cafilon | Yamanouchi | Japan | — |
| Marsin | Ikapharm | Israel | — |

**Raw Materials**

Bromopropiophenone
Hydrogen
Benzyl ethanolamine
Hydrogen chloride

**Manufacturing Process**

10 grams of β-phenyl-α-methyl-β,β'-dihydroxy-diethylamine hydrochloride (produced by hydrogenation in the presence of palladium and charcoal of β-phenyl-α-methyl-β-keto-β'-hydroxy-N-benzyl-diethylamine hydrochloride obtained from bromopropiophenone by reacting with benzyl-ethanolamine), are warmed with 10% hydrochloric acid for 6 hours on a water bath.

After working up in the usual manner, the hydrochloride of the 2-phenyl-3-methyl-morpholine crystallizes out from methanolic hydrochloric acid and acetone, MP = 182°C, according to U.S. Patent 2,835,669.

**References**

Merck Index 7108
Kleeman & Engel p. 714
PDR p. 678
OCDS Vol. 1 p. 260 (1977)
I.N. p. 757
REM p. 892

Thoma, O.; U.S. Patent 2,835,669; May 20, 1958; assigned to C.H. Boehringer Sohn, Germany

Siemer, H. and Hengen, O.; U.S. Patent 3,018,222; January 23, 1962; assigned to Ravensberg GmbH, Germany

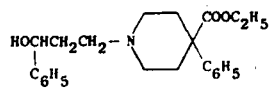
# PHENOPERIDINE HYDROCHLORIDE

**Therapeutic Function:** Analgesic

**Chemical Name:** 1-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-piperidinecarboxylic acid ethyl ester hydrochloride

**Common Name:** 3-(4-carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol hydrochloride

**Structural Formula:**




(base)

**Chemical Abstracts Registry No.:** 3627-49-4; 562-26-5 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Operidine | Janssen | U.S. | 1965 |
| Lealgin | Leo | Sweden | — |
| R-1406 | Le Brun | France | — |

**Raw Materials**

Phenylacetonitrile
Bis-Chloroethyl toluene sulfonyl amide
Benzoylethylene
Hydrogen

**Manufacturing Process**

The starting materials for the overall process are phenylacetonitrile with bis-chloroethyl toluene sulfonyl amide. These react to give a product which hydrolyzes to normeperidine (4-carboethoxy-4-phenylpiperidine). Condensation of that material with benzoylethylene gives the ketone: β-(4-carboethoxy-4-phenylpiperidino)propiophenone.

A reaction mixture was prepared containing 4 grams of β-(4-carboethoxy-4-phenylpiperidino)-propiophenone hydrochloride, 100 ml of methanol and about 0.5 gram of platinum oxide catalyst. The mixture was placed in a low pressure hydrogenation apparatus and was hydrogenated at a temperature of about 27°C and a pressure of about 3.5 atmospheres of hydrogen to convert the keto group of the β-(4-carboethoxy-4-phenylpiperidino)-propiophenone to a hydroxy group, and to form 3-(4-carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol hydrochloride. After the hydrogenation was complete, the catalyst was separated from the reaction mixture by filtration, and the filtrate was evaporated to dryness in vacuo leaving a residue containing 3-(4-carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol hydrochloride. The residue was digested with ethyl acetate thereby causing 3-(4-carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol hydrochloride to crystallize. This compound melted at about 188°-189°C after being recrystallized three times from an ethyl acetate-methanol solvent mixture, according to U.S. Patent 2,951,080.

**References**

Merck Index 7125
Kleeman & Engel p. 715
OCDS Vol. 1 p. 302 (1977)
I.N. p. 759

Pohland, A.; U.S. Patent 2,951,080; August 30, 1960; assigned to Eli Lilly and Company
Cutler, F.A., Jr. and Fisher, J.F.; U.S. Patent 2,962,501; November 29, 1960; assigned to Merck & Co., Inc.

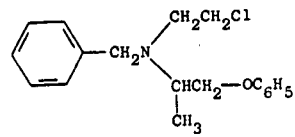
## PHENOXYBENZAMINE HYDROCHLORIDE

**Therapeutic Function:** Adrenergic blocker

**Chemical Name:** N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)benzenemethanamine hydrochloride

**Common Name:** —

**Structural Formula:**



**Chemical Abstracts Registry No.:** 63-92-3; 59-96-1 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Dibenzyline | SKF | U.S. | 1953 |
| Dibenzyran | Rohm Pharma | W. Germany | — |

**Raw Materials**

1-Phenoxy-2-propanol
Ethanolamine
Hydrogen chloride
Thionyl chloride
Benzyl chloride

**Manufacturing Process**

*Step 1:* In a 500 ml flask equipped with gas inlet tube, dropping funnel and reflux condenser is placed 139 grams of 1-phenoxy-2-propanol. A stream of dry air is bubbled through the alcohol while 55 grams of thionyl chloride is added dropwise with external cooling. The stream of dry air is continued for about six hours or until most of the hydrogen chloride has been expelled and then another 55 grams of thionyl chloride is added. The reaction mixture is allowed to stand twenty-four hours, a few drops of pyridine are added and the mixture heated 4 hours on the steam bath. The cooled reaction mixture is poured into water, the crude product is washed with dilute sodium bicarbonate solution and finally taken up in benzene. The benzene is distilled at ordinary pressure and the residue distilled in vacuo to yield 60-70% of 1-phenoxy-2-chloropropane, BP 93°-94°C/5 mm.

*Step 2:* To 494 grams of ethanolamine, heated to approximately 150°C in a 500 ml flask equipped with stirrer, condenser and dropping funnel, is added 465 grams of 1-phenoxy-2-chloropropane with mechanical stirring. The reaction mixture is then heated to reflux for 3 hours, cooled and poured into a liter of water. The organic layer is extracted into ether and the ether solution is extracted with dilute hydrochloric acid. The aqueous acid solution is then made alkaline with 40% sodium hydroxide solution and the organic base is extracted into ether. Removal of the ether leaves N-(phenoxyisopropyl)-ethanolamine which, after recrystallization from hexane, melts at 70.5°-72°C.

*Step 3:* To 43 grams of N-(phenoxyisopropyl)ethanolamine dissolved in 500 ml of alcohol in a 1,000 ml flask equipped with stirrer and condenser is added 28 grams of benzyl chloride and 18.5 grams of sodium bicarbonate. The mixture is stirred and refluxed for 10 hours and then approximately half the alcohol is removed by distillation. The remaining solution is poured into 500 ml of water and the organic material extracted with 3 100-ml portions of ether. The combined ether extracts are washed with water, dried over anhydrous potassium carbonate and filtered. After removal of the ether, the residue is distilled in vacuo to yield N-(phenoxyisopropyl)-N-benzylethanolamine, BP 163°-168°C/0.2 mm.

*Step 4:* A solution of 20 grams of the above amino alcohol is dissolved in 50 ml of dry chloroform and treated with dry hydrogen chloride until acid. Then a solution of 9 grams of thionyl chloride in 50 ml of dry chloroform is added and the reaction mixture is heated on a water bath at 50°-60°C for 2 hours. Most of the chloroform is removed by distillation under reduced pressure. Addition of ether to the residue causes the product to crystallize. After recrystallization from a mixture of alcohol and ether, the N-(phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochloride melts at 137.5°-140°C.

**References**

Merck Index 7134
Kleeman & Engel p. 716
PDR p. 1713
OCDS Vol. 1 p. 55 (1977)
I.N. p. 760
REM p. 905

Kerwin, J.F. and Ullyot, G.E.; U.S. Patent 2,599,000; June 3, 1952; assigned to Smith, Kline & French Laboratories

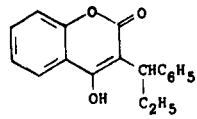
# PHENPROCOUMON

**Therapeutic Function:** Anticoagulant

**Chemical Name:** 4-hydroxy-3-(1-phenylpropyl)-2H-1-benzopyran-2-one

**Common Name:** 3-(1-phenylpropyl)-4-hydroxycoumarin

**Structural Formula:**




**Chemical Abstracts Registry No.:** 435-97-2

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Liquamar | Organon | U.S. | 1958 |
| Falithrom | Fahlberg-List | E. Germany | — |
| Fencumar | Medica | Finland | — |
| Marcumar | Roche | W. Germany | — |

**Raw Materials**

Diethyl-(1'-phenylpropyl)malonate
Acetylsalicylic acid chloride
Methanol
Sodium
Sodium hydroxide

**Manufacturing Process**

8.3 parts by weight of powdered sodium in 300 parts by volume of benzene, 100 parts by weight of diethyl (1'-phenylpropyl)-malonate and 72 parts by weight of acetylsalicylic acid chloride are reacted together to form diethyl 1-(o-acetoxybenzoyl)-1-(1'-phenylpropyl)-malonate, which boils at 195°-198°C/0.03 mm Hg.

10.3 parts of weight of diethyl 1-(o-acetoxybenzoyl)-1-(1'-phenylpropyl)-malonate are dissolved in 60 parts by volume of absolute ether and to this solution are added portionwise at 10°C, while stirring, 2.6 parts by weight of sodium methylate. The reaction mixture is stirred for 4 hours, whereupon it is poured into ice water. The ether solution is washed neutral with ice water. After having distilled off the ether, a thick oil consisting of 3-carbethoxy-3-(1'-phenylpropyl)-4-oxo-dihydrocoumarin is obtained. This compound crystallized in butyl oxide and has a MP of 108°-109°C.

The 3-carbethoxy-3-(1'-phenylpropyl)-4-oxo-dihydrocoumarin may be hydrolyzed and decarboxylated as follows. The crude product is heated to 85°C for ½ hour with 100 parts by volume of 5% aqueous sodium hydroxide, while agitating or stirring. To remove traces of undissolved oil, the cooled solution is treated with 1 part by weight of charcoal, whereupon it is filtrated and acidified to Congo reaction with dilute sulfuric acid. The 3-(1'-phenylpropyl)-4-hydroxycoumarin formed is separated off and recrystallized in 80% ethanol, whereupon it melts at 178°-179°C according to U.S. Patent 2,701,804.

**References**

Merck Index 7139
Kleeman & Engel p. 718
I.N. p. 761
REM p. 827
Hegedüs, B. and Grüssner, A.; U.S. Patent 2,701,804; February 8, 1955; assigned to Hoffmann-La Roche Inc.
Schroeder, C.H. and Link, K.P.; U.S. Patent 2,872,457; February 3, 1959; assigned to Wisconsin Alumni Research Foundation
Preis, S., West, B.D. and Link, K.P.; U.S. Patent 3,239,529; March 8, 1966; assigned to Wisconsin Alumni Research Foundation

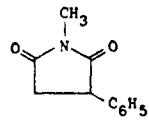
# PHENSUXIMIDE

**Therapeutic Function:** Anticonvulsant

**Chemical Name:** 1-methyl-3-phenyl-2,5-pyrrolidinedione

**Common Name:** N-methyl-α-phenylsuccinimide

**Structural Formula:**



**Chemical Abstracts Registry No.:** 86-34-0

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Milontin | Parke Davis | U.S. | 1953 |
| Lifene | Debat | France | — |
| Petimid | Dincel | Turkey | — |
| Succitimal | Katwijk | Neth. | — |

**Raw Materials**

Phenylsuccinic anhydride
Methyl amine
Acetyl chloride

**Manufacturing Process**

10 grams of phenylsuccinic anhydride is dissolved in 250 ml of absolute ether and the solution is treated with dry methylamine until a precipitate ceases to form. After standing for ½ hour the ether is decanted off and the residue is washed with 40 ml of water by decantation. The mixture is filtered and the precipitate washed with 10 ml of water. By acidification of the filtrate, a white precipitate is obtained. After drying it weighs 8 grams and melts at 136°-140°C. The two precipitates are combined and recrystallized from aqueous alcohol to give β-N-methylphenylsuccinamic acid which melts at 158°-160°C.

9 grams of β-N-methylphenylsuccinamic acid and 200 ml of acetyl chloride are heated together on a steam bath for ½ hour. The excess acetyl chloride is removed by distillation and 50 ml of water are added to the thick residue. After allowing for hydrolysis of

the excess acetyl chloride the water is decanted and the yellow residue dissolved in 75 ml of ether. The resulting solution is treated with charcoal twice and dried over anhydrous magnesium sulfate. On partial evaporation of the ether a white solid precipitates. There is obtained 4 grams of N-methyl-α-phenylsuccinimide which melts at 71°-73°C.

**References**

Merck Index 7140
Kleeman & Engel p. 718
PDR p. 1367
OCDS Vol. 1 p. 226 (1977)
I.N. p. 762
REM p. 1080
Miller, C.A. and Long, L.M.; U.S. Patent 2,643,258; June 23, 1953; assigned to Parke, Davis & Company

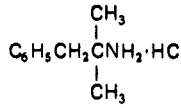
## PHENTERMINE HYDROCHLORIDE

**Therapeutic Function:** Antiobesity drug

**Chemical Name:** α,α-dimethylbenzeneethanamine hydrochloride

**Common Name:** α-benzylisopropylamine hydrochloride; phenyl-tert-butylamine hydrochloride

**Structural Formula:**



**Chemical Abstracts Registry No.:** 1197-21-3; 122-09-8 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Wilpo | Dorsey | U.S. | 1961 |
| Linyl | Roussel | France | 1962 |
| Fastin | Beecham | U.S. | 1973 |
| Adipex-P | Lemmon | U.S. | 1976 |
| Ona Mast | Mast | U.S. | 1980 |
| Obestin | Ferndale | U.S. | 1980 |
| Oby-Trim | Rexar | U.S. | 1982 |
| Duromine | Riker | U.K. | — |
| Ex-Adipos | Eurand | Italy | — |
| Ionamin | Pennwalt | U.K. | — |
| Jonakraft | Kraft Pharm | U.S. | — |
| Lipopil | Roussel Maestretti | Italy | — |
| Minobese | Restan | S. Africa | — |
| Mirapront | Bracco | Italy | — |
| Netto-Longcaps | Heyden | W. Germany | — |
| Panbesy | Asperal | Belgium | — |
| Panshade | Pan American | U.S. | — |
| Parmine | Parmed | U.S. | — |
| Phentermine | Schein | U.S. | — |
| Phentermyl | Diethelm | W. Germany | — |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Regulin | Kwizda | Austria | – |
| Span R/D | Metro Med | U.S. | – |
| Teramine | Legere | U.S. | – |

**Raw Materials**

Isobutyryl chloride
Ammonia
Hydrogen chloride
Bromine
Calcium hydroxide
Sodium
Benzyl bromide
Benzene
Potassium hydroxide

**Manufacturing Process**

*Preparation of Isobutyrophenone:* In a 12 liter, 3-necked flask, 1,280 grams of aluminum chloride was covered with 2,000 cc of dry thiophene-free benzene and a solution of 919 grams of isobutyryl chloride, (BP 92°-94°C) in 1 liter of benzene was added slowly with stirring. After heating for 3 hours at reflux, the solution was cooled and poured over a mixture of 1 liter of concentrated hydrochloric acid and 5 kg of ice. The benzene layer was separated, the aqueous layer extracted with benzene, and the combined benzene solutions were washed, dried and concentrated in vacuo. The residue was distilled rapidly to give 1,051 grams of isobutyrophenone, boiling at 81°-89°C at 1 mm, yield 83.4%.

*Preparation of 1,3-Diphenyl-2,2-Dimethylpropanone-1:* Sodamide was prepared from 12.5 grams of sodium added in small portions to 600 cc of liquid ammonia with 1 gram of hydrous ferric chloride as catalyst. The ammonia was replaced by 200 cc of dry toluene and without delay a solution of 74 grams of isobutyrophenone and 76.5 grams of benzyl bromide in 200 cc of benzene was slowly added with stirring. The reaction mixture was heated on a boiling water bath for 48 hours. Water was then added, the organic layer separated and the product isolated by distillation. The 1,3-diphenyl-2,2-dimethylpropanone-1 boiled from 142°-143°C at a pressure of 3 mm, $n_D^{20}$ 1.5652.

*Preparation of α,α-Dimethyl-β-Phenylpropionamide:* Sodamide was prepared from 7.6 grams of sodium in 350 cc of liquid ammonia with 0.9 gram of hydrous ferric chloride. The ammonia was replaced by 250 cc of toluene, the mixture was heated to 60°C and 71.4 grams of 1,3-diphenyl-2,2-dimethyl propanone-1 dissolved in 150 cc of toluene was added. The mixture was stirred and heated on a steam bath for 5 hours. A clear red color appeared in 15 minutes and disappeared after about an hour. After cooling, water was added, the organic layer was washed, dried, and concentrated to give 36.5 grams of α,α-dimethyl-β-phenyl propionamide which crystallized slowly after the addition of an equal volume of petroleum ether. The product melted at 62°C after crystallization from benzene-petroleum ether.

*Preparation of Di-(β-Phenyl-α,α-Dimethylethyl)Urea:* 3.5 grams of α,α-dimethyl-β-phenyl-propionamide in 420 cc of water was added to a solution of 87.5 grams of potassium hydroxide and 35 grams of bromine in 350 cc of water. After 2 hours at 60°C, the product was obtained on crystallization from ethanol, melting at 184°C.

*Preparation of ω-Phenyl-tert-Butylamine:* 24 grams of the urea derivative obtained as indicated above, were well mixed with 96 grams of calcium hydroxide in a flask immersed in an air bath and provided with a dropping funnel the stem of which reached the bottom of the flask. The mixture was heated to 240°-260°C (inside temperature) for 7 hours during which time 86 cc of water was slowly added. The vapors were collected in a receiver cooled with ice. After extraction with ether and distillation, the product was obtained as a colorless liquid boiling from 80°-84°C at 9 mm according to U.S. Patent 2,590,079.

The ether solution may be dried and saturated with hydrogen chloride and the precipitated hydrochloride recrystallized from a mixture of 50 parts alcohol and 100 parts of acetone.

The pure hydrochloride is thus obtained as a white crystalline substance having a MP of 195°-196°C, according to U.S. Patent 2,408,345.

**References**

Merck Index 7141
Kleeman & Engel p. 719
PDR pp. 660, 1033, 1034, 1246, 1450, 1606, 1999
OCDS Vol. 1 p. 72 (1977)
I.N. p. 762
REM p. 892
Shelton, R.S. and Van Campen, M.G., Jr.; U.S. Patent 2,408,345; September 24, 1946; assigned to The Wm. S. Merrell Company
Abell, L.L., Bruce, W.F. and Seifter, J.; U.S. Patent 2,590,079; March 25, 1952; assigned to Wyeth Incorporated

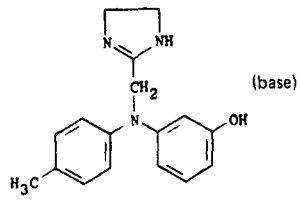
## PHENTOLAMINE HYDROCHLORIDE

**Therapeutic Function:** Adrenergic blocker

**Chemical Name:** 3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl] (4-methylphenyl)amino] phenol hydrochloride

**Common Name:** 2-(m-hydroxy-N-p-tolylanilinomethyl)-2-imidazoline hydrochloride

**Structural Formula:**




**Chemical Abstracts Registry No.:** 73-05-2; 50-60-2 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Regitine | Ciba | U.S. | 1952 |
| Regitine | Ciba-Geigy-Takeda | Japan | — |
| Rogitine | Ciba | U.K. | — |

**Raw Materials**

N-(p-Methylphenyl)-m'-hydroxyphenylamine
2-Chloromethylimidazoline HCl
Hydrogen chloride

**Manufacturing Process**

199.24 parts of N-(p-methylphenyl)-m'-hydroxyphenylamine and 77.52 parts of 2-chloromethylimidazoline hydrochloride are heated for sixteen hours in an oil bath having a temperature of 150°C, while stirring and introducing a current of nitrogen. The viscous contents of the flask are then cooled to about 100°C, mixed with 400 parts by volume of hot water, and stirred for a short time.

After further cooling to about 60°C, 200 parts by volume of water and 500 parts by volume of ethyl acetate at 60°C are added, and the aqueous layer is separated. The excess of starting material may be recovered from the ethyl acetate.

The aqueous portion is chilled in a cooling chamber at -10°C, whereupon the hydrochloride of 2-[N-(p-methylphenyl)-N-(m'-hydroxyphenyl)-aminomethyl]-imidazoline crystallizes. Upon being concentrated and cooled the mother liquor yields a further quantity of the hydrochloride. The combined quantities of hydrochloride are treated with a small quantity of cold water, dried with care, and washed with ethyl acetate. The product is then crystallized from a mixture of alcohol and ethyl acetate, and there is obtained a hydrochloride melting at 239°-240°C.

**References**

Merck Index 7143
Kleeman & Engel p. 719
PDR p. 809
OCDS Vol. 1 p. 242 (1977)
I.N. p. 762
REM p. 906
Miescher, K., Marxer, A. and Urech, E.; U.S. Patent 2,503,059; April 4, 1950; assigned to Ciba Pharmaceutical Products, Inc.

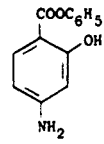
# PHENYL AMINOSALICYLATE

**Therapeutic Function:** Antibacterial (Tuberculostatic)

**Chemical Name:** 4-Amino-2-hydroxybenzoic acid phenyl ester

**Common Name:** Fenamisal

**Structural Formula:**




**Chemical Abstracts Registry No.:** 133-11-9

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Pheny-Pas-Teb-Amin | Purdue Frederick | U.S. | 1959 |
| Fenil-PAS | Farmabion | Spain | — |

**Raw Materials**

p-Nitrosalicylic acid
Phosphorus oxychloride
Phenol
Hydrogen

**Manufacturing Process**

183 g of p-nitrosalicylic acid are dissolved in 564 g of phenol by heating to 140°C to 150°C on an oil bath. When all the p-nitrosalicylic acid is dissolved, 153 g of phosphorus oxychloride are run in, drop by drop, over a period of about 2 hours, while maintaining the tempera-

ture at about 150°C. The still warm mixture is run into 2 liters of water with agitation. The precipitate formed is filtered off, washed with water until phenol is removed and then dried.

There are thus obtained 250 g of 2-hydroxy-4-nitrophenylbenzoate which melts at 154°C to 155°C.

In a hydrogenation autoclave are introduced 92 g of 2-hydroxy-4-nitrophenylbenzoate preceded by 200 cc of ethyl acetate; Raney nickel, obtained from 30 g of alloy, is added with 300 cc of ethyl acetate. Hydrogenation under pressure (100 to 120 kg) at ordinary temperature is carried out during a period of about 12 hours. The nickel is filtered off and the ethyl acetate is removed by distillation on the water bath under a vacuum of 300 mm. There is thus obtained 80 g of crude damp 2-hydroxy-4-aminophenylbenzoate which after recrystallization from isopropyl alcohol melts at 153°C.

**References**

Merck Index 7151
OCDS Vol. 2 p. 89 (1980)
I.N. p. 415
Freire, S.A.; U.S. Patent 2,604,488; July 22, 1952; assigned to Soc. des Usines Chimiques Rhone-Poulenc (France)

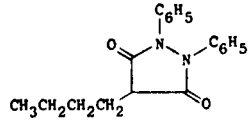
## PHENYLBUTAZONE

**Therapeutic Function:** Antiinflammatory; antiarthritic

**Chemical Name:** 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione

**Common Name:** 3,5-dioxo-1,2-diphenyl-4-n-butylpyrazolidine

**Structural Formula:**



**Chemical Abstracts Registry No.:** 50-33-9

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Butazolidin | Geigy | U.S. | 1952 |
| Butazolidin | Ciba Geigy | France | 1954 |
| Azolid | U.S.V. Pharm | U.S. | 1971 |
| Acrizeal | S.S. Pharm | Japan | – |
| Alkabutazona | Lovens | Denmark | – |
| Anuspiramin | Farbios | Spain | – |
| Artropan | Polifarma | Italy | – |
| Bulentin | Sanwa | Japan | – |
| Butacal | Langley | Australia | – |
| Butacote | Geigy | U.K. | – |
| Butadion | Streuli | Switz. | – |
| Butadiona | Miquel | Spain | – |
| Butadyne | Bio-Chimique | Canada | – |
| Butalan | Lancet | Australia | – |
| Butalgin | Fawns & McAllan | Australia | – |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Butalgina | Esteve | Spain | – |
| Butaluy | Miluy | Spain | – |
| Butaphen | Mulda | Turkey | – |
| Butapirazol | Polfa | Poland | – |
| Butarex | Adams | Australia | – |
| Butartril | Chiesi | Italy | – |
| Butazina | Vis | Italy | – |
| Butazone | DDSA | U.K. | – |
| Butiwas Simple | Wassermann | Spain | – |
| Butoroid | Virax | Australia | – |
| Butrex | SCS Pharmalab | S. Africa | – |
| Carudol | Lab. Franc. Therap. | France | – |
| Chembuzone | Chemo-Drug | Canada | – |
| Demoplas | Adenylchemie | W. Germany | – |
| Digibutina | Bicsa | Spain | – |
| Diossidone | Eliovit | Italy | – |
| Ecobutazone | I.C.N. | Canada | – |
| Elmedal | Thiemann | W. Germany | – |
| Equi Bute | Fort Dodge Labs | U.S. | – |
| Eributazone | Eri | Canada | – |
| Fenibutasan | Santos | Spain | – |
| Fenibutol | Atral | Portugal | – |
| Flexazone | Berk | U.K. | – |
| IA-But | Inter-Alia | U.K. | – |
| Intalbut | Inter-Alia | U.K. | – |
| Kadol | Midi | Italy | – |
| Merizone | Meriot | Canada | – |
| Neo-Zoline | Neo | Canada | – |
| Neuplus | Toyo | Japan | – |
| Novobutazone | Novopharm | Canada | – |
| Novophenyl | Novopharm | Canada | – |
| Panazone | Propan-Lipworth | S. Africa | – |
| Phenbutazol | Smallwood | Canada | – |
| Phenyl Betazone | Barlow Cote | Canada | – |
| Phenylone | Medic | Canada | – |
| Pilazon | Kobayashi | Japan | – |
| Pirarreumol | Hermes | Spain | – |
| Praecirheumin | Pfleger | W. Germany | – |
| Rectofasa | Lifasa | Spain | – |
| Reumasyl | Leiras | Finland | – |
| Reumazin | Mohan | Japan | – |
| Reumuzol | Farmos | Finland | – |
| Reupolar | Farmos | Finland | – |
| Rheumaphen | Reiss | W. Germany | – |
| Schemergen | Azusa | Japan | – |
| Sedazole | Toho | Japan | – |
| Servizolidin | Servipharm | Switz. | – |
| Shigrodin | Ikapharm | Israel | – |
| Spondyril | Dorsch | W. Germany | – |
| Tetnor | Drugs, Ltd. | U.K. | – |
| Tevcodyne | Tevcon | U.S. | – |
| Therazone | Western Serum | U.S. | – |
| Ticinil | De Angeli | Italy | – |
| Todalgil | Lopez-Brea | Spain | – |
| Tokugen | Sawai | Japan | – |
| Uzone | Kempthorne Prosser | New Zealand | – |
| Wescozone | Saunders | Canada | – |
| Zolidinium | Kwizda | Austria | – |

**Raw Materials**

Hydrazobenzene
Sodium
Diethyl-n-butyl malonate
Ethanol

**Manufacturing Process**

7.6 parts of sodium are dissolved in 190 parts by volume of absolute alcohol; 65 parts of diethyl-n-butyl malonate and 55 parts of hydrazobenzene are added. The alcohol is slowly distilled off and the reaction mixture heated for 12 hours at a bath temperature of 150°C and finally in vacuo, until no more alcohol comes off.

The product is dissolved in water, clarified with a little animal charcoal and 15% hydrochloric acid is slowly added until an acid reaction to Congo red paper is produced. 1,2-Diphenyl-3,5-dioxo-4-n-butyl-pyrazolidine separates as an oil, which rapidly become crystalline. It crystallizes from alcohol as colorless needles with a MP of 105°C.

**References**

Merck Index 7157
Kleeman & Engel p. 720
PDR pp. 830, 891, 1606, 1999
OCDS Vol. 1 p. 236 (1977) & 2, 388, 474 (1980)
I.N. p. 763
REM p. 1120
Stenzl, H.; U.S. Patent 2,562,830; July 31, 1951; assigned to J.R. Geigy AG, Switzerland

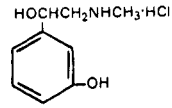
# PHENYLEPHRINE HYDROCHLORIDE

**Therapeutic Function:** Adrenergic

**Chemical Name:** (R)-3-Hydroxy-α-[(methylamino)methyl] benzenemethanol hydrochloride

**Common Name:** m-Methylaminoethanolphenol hydrochloride; metaoxedrin

**Structural Formula:**




**Chemical Abstracts Registry No.:** 61-76-7

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Neosynephrine | Badrial | France | 1953 |
| Mydfrin | Alcon | U.S. | 1979 |
| Nostril | Boehr. Ingel | U.S. | 1982 |
| Adrianol | Anasco | W. Germany | – |
| Atrohist | Adams | U.S. | – |
| Bromphen | Schein | U.S. | – |
| Codimal | Central | U.S. | – |
| Comhist | Norwich-Eaton | U.S. | – |
| Congespirin | Bristol-Myers | U.S. | – |
| Coryban | Pfipharmecs | U.S. | – |
| Dallergy | Laser | U.S. | – |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Deconsal | Adams | U.S. | – |
| Decontabs | Zenith | U.S. | – |
| Degest | Barnes-Hind | U.S. | – |
| Derizene | Hollister-Stier | U.S. | – |
| Donatussin | Laser | U.S. | – |
| Dristan | Whitehall | U.S. | – |
| Dura-Vent | Dura | U.S. | – |
| E.N.T. | Springbok | U.S. | – |
| Entex | Norwich Eaton | U.S. | – |
| Extendryl | Fleming | U.S. | – |
| Fenilfar | Farmila | Italy | – |
| Histalet | Reid-Rowell | U.S. | – |
| Histamic | Metro Med | U.S. | – |
| Histaspan | U.S.V. Pharm | U.S. | – |
| Histor | Hauck | U.S. | – |
| Hycomine | Du Pont | U.S. | – |
| Isonefrine | Tubi Lux Farma | Italy | – |
| Isophrine | Broemmel | U.S. | – |
| Isotropina | Tubi Lux Farma | Italy | – |
| Korigesic | Trimen | U.S. | – |
| Matafa-Lind | Anasco | W. Germany | – |
| Naldecon | Bristol | U.S. | – |
| Nasophen | Premo | U.S. | – |
| Neosinefrina | Reunidos | Spain | – |
| Newphrine | Vitarine | U.S. | – |
| Nostril | Boehr. Ingel | U.S. | – |
| Pediacof | Winthrop-Breon | U.S. | – |
| Phenergan | Wyeth | U.S. | – |
| Protid | La Salle | U.S. | – |
| PV-Tussin | Reid-Rowell | U.S. | – |
| Quelidrine | Abbott | U.S. | – |
| Rinisol | Farmos | Finland | – |
| Ru-Tuss | Boots | U.S. | – |
| Singlet | Lakeside | U.S. | – |
| S-T Forte | Scot-Tussin | U.S. | – |
| Synasal | Texas Pharmacal | U.S. | – |
| Tear-Efrin | Tilden Yates | U.S. | – |
| Tussar | U.S.V. Pharm. | U.S. | – |
| Tussirex | Scot-Tussin | U.S. | – |
| Tympagesic | Adria | U.S. | – |
| Visopt | Sigma | Australia | – |
| Zeph | Scott & Turner | Australia | – |

**Raw Materials**

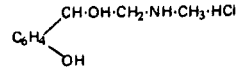
m-Hydroxymethylaminoacetophenone
Hydrogen
Hydrogen chloride

**Manufacturing Process**

4.5 g of the hydrochloride of m-hydroxymethylaminoacetophenone are dissolved in a small amount of water; to the solution a solution of colloidal palladium obtained from palladium-chloride is added, and the mixture is treated with hydrogen.

After diluting the reaction liquid with acetone it is filtered, and the residue obtained after the evaporation of the filtrate in vacuo, and complete drying over pentoxide of phosphorus is then dissolved in absolute alcohol, and to this is added about the same volume of dry ether,

until turbidity just commences to occur. After a short time the hydrochloride of the m-hydroxyphenylethanol-methylamine of the formula



will separate out as a colorless mass of crystals at a melting point of 142°C to 143°C.

**References**

Merck Index 7167
PDR pp. 555, 562, 570, 677, 688, 701, 727, 784, 855, 865, 880, 928, 991, 1246, 1272, 1276, 1404, 1447, 1606, 1662, 1735, 1807, 1813, 1824, 1899, 1923, 1973, 1999
OCDS Vol. 1 p. 63 (1977); 2, 265 (1980) & 3, 20 (1984)
I.N. p. 764
REM p. 889
Legerlotz, H.; U.S. Patent 1,932,347; October 24, 1933; assigned to Frederick Stearns & Co.

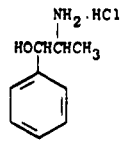
## PHENYLPROPANOLAMINE HYDROCHLORIDE

**Therapeutic Function:** Nasal decongestant; anorexic

**Chemical Name:** α-(1-aminoethyl)benzenemethanol hydrochloride

**Common Name:** dl-norephedrine hydrochloride; 2-amino-1-phenyl-1-propanol hydrochloride

**Structural Formula:**



**Chemical Abstracts Registry No.:** 154-41-6; 492-41-1 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Propadrine | MSD | U.S. | 1941 |
| Dexatrim | Thompson | U.S. | 1980 |
| Dietac | Menley James | U.S. | 1980 |
| Obestat | Lemmon | U.S. | 1980 |
| Permatrim | Lee | U.S. | 1980 |
| Nobese | O'Neal, Jones | U.S. | 1981 |
| Dexatrim Extra | Thompson | U.S. | 1981 |
| Propagest | Carnrick | U.S. | 1982 |
| Acutrim | Ciba Geigy | U.S. | 1983 |
| Help | Verex | U.S. | 1983 |
| Appedrine | Thompson | U.S. | – |
| Bromphen | Schein | U.S. | – |
| Codimal | Central | U.S. | – |
| Comtrex | Bristol-Myers | U.S. | – |
| Congespirin | Bristol-Myers | U.S. | – |
| Control | Thompson | U.S. | – |
| Corvban-D | Pfipharmecs | U.S. | – |
| Co-Tylenol | McNeil | U.S. | – |

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Cremacoat | Vicks | U.S. | – |
| Decontabs | Zenith | U.S. | – |
| Dietrim | Legere | U.S. | – |
| Dimetane-D.C. | Robins | U.S. | – |
| Dura Vent | Dura | U.S. | – |
| E.N.T. | Springbok | U.S. | – |
| Entex | Norwich Eaton | U.S. | – |
| Fiogesic | Sandoz | U.S. | – |
| Head & Chest | Procter & Gamble | U.S. | – |
| Histaminic | Metro Med | U.S. | – |
| Hycomine | Du Pont | U.S. | – |
| Korigesic | Trimen | U.S. | – |
| Kronohist | Ferndale | U.S. | – |
| Monydrin | Draco | Sweden | – |
| Naldecon | Bristol | U.S. | – |
| Nolamine | Carnrick | U.S. | – |
| Ornade | SKF | U.S. | – |
| Poly-Histine | Bock | U.S. | – |
| Prolamine | Thompson | U.S. | – |
| Rhindecon | McGregor | U.S. | – |
| Rhinolar | McGregor | U.S. | – |
| Ru-Tuss | Boots | U.S. | – |
| Sinubid | Parke Davis | U.S. | – |
| Sinulin | Carnrick | U.S. | – |
| Tinaroc | Remeda | Finland | – |
| Triaminic | Dorsey | U.S. | – |
| Tuss-Ornade | SKF | U.S. | – |

**Raw Materials**

Benzaldehyde
Nitroethane
Hydrogen chloride
Sodium bisulfite
Hydrogen

**Manufacturing Process**

In one route as described in U.S. Patent 2,151,517, 10.7 kg of technical benzaldehyde is vigorously agitated with a solution of 11.0 kg of sodium bisulfite in 50.0 liters of water until the formation of the addition-product is complete. Simultaneously, 8.25 kg of nitroethane is dissolved in a solution of 4.5 kg of caustic soda in 20.0 liters of water and the resultant warm solution is added with vigorous stirring to the magma of benzaldehyde sodium bisulfite. The mixture is agitated for 30 minutes and then allowed to stand overnight.

The aqueous portion of the mixture is now siphoned off from the supernatant layer of oily phenylnitropropanol and replaced with a fresh solution of 11.0 kg of sodium bisulfite in 50.0 liters of water. The mixture of phenylnitropropanol and bisulfite solution is now vigorously agitated for 15 minutes in order to remove and recover small amounts of unreacted benzaldehyde, and is then again allowed to stratify. This time, the phenylnitropropanol is siphoned off and filtered to remove a small amount of resinous material. The aqueous solution of sodium bisulfite remaining behind is reacted with benzaldehyde, as described above, thus making the process continuous.

The 1-phenyl-2-nitropropanol thus obtained is a colorless oil, specific gravity 1.14 at 20°C, odorless when pure, volatile with steam and boiling at 150° to 165°C under a pressure of 5 mm of mercury. It is soluble in alcohol, ether, acetone, chloroform, carbon tetrachloride, benzene and glacial acetic acid. The yield of 1-phenyl-2-nitropropanol obtained by this procedure is 17.1 to 17.7 kg.

It is hydrogenated and converted to the hydrochloride in subsequent steps. The hydrogen chloride has a melting point of 192°-194°C.

In an alternative route described in U.S. Patent 3,028,429 propiophenone may be reacted with an alkyl nitrite to give isonitrosopropiophenone which is then hydrogenated and finally converted to the hydrochloride.

**References**

Merck Index 7189
Kleeman & Engel p. 721
PDR pp. 674, 688, 702, 727, 781, 784, 850, 854, 865, 875, 1033, 1084, 1246, 1277, 1388, 1404, 1431, 1454, 1583, 1606, 1719, 1730, 1735, 1805, 1807, 1869, 1999
I.N. p. 766
REM p. 889
Kamlet, J.; U.S. Patent 2,151,517 March 21, 1939
Wilbert, G. and Sosis, P.; U.S. Patent 3,028,429; April 3, 1962; assigned to Nepera Chemical Co., Inc.

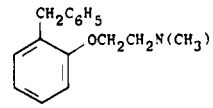
## PHENYLTOLOXAMINE

**Therapeutic Function:** Antihistaminic

**Chemical Name:** N,N-Dimethyl-2-[2-(phenylmethyl)phenoxy] ethanamine

**Common Name:** Bistrimin

**Structural Formula:**




**Chemical Abstracts Registry No.:** 92-12-6; 6152-43-8 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Bristalin | Bristol | U.S. | 1952 |
| Bristamine | Banyu | Japan | — |
| Codipront | Mack | W. Germany | — |
| Ephepect | Bolder | W. Germany | — |
| Floxamine | Durst | U.S. | — |
| Fluidol | Metadier-Tours | France | — |
| Histionex | Strasenburgh | U.S. | — |
| Netux | Roussel | France | — |
| Pholtex | Riker | U.K. | — |
| Quadrahist | Schein | U.S. | — |
| Rinurel | Warner | U.K. | — |
| Tussionex | Pennwalt | U.S. | — |

**Raw Materials**

o-Benzylphenol
Methanol
Sodium
Dimethylaminoethyl chloride

**Manufacturing Process**

Sodium methylate is made by dropping 11.7 g of sodium strips into 199 ml of absolute methanol in a 1-liter three-necked flask. 93.9 g of o-benzylphenol are dissolved in 200 ml of dry toluene and added to the sodium methylate solution. The solution is distilled until the boiling point of toluene is reached. At the end of the distillation, enough toluene is added to restore the original volume of solvent.

109.5 g of dimethylaminoethyl chloride hydrochloride and 200 ml of toluene are placed in a 1-liter Erlenmeyer flask, cooled in an ice bath, and decomposed with 167.5 g of 20% sodium hydroxide solution. The toluene and water layers are separated, and the water layer is extracted again with 50 ml of toluene. The toluene layers are combined, washed with saturated salt solution, and dried over anhydrous potassium carbonate.

The dried dimethylaminoethyl chloride solution is poured into the toluene solution of the sodium salt of o-benzylphenol, heated to reflux, and refluxed 16 hours. After refluxing, enough water is added to the mixture to dissolve the precipitated solid. The layers are separated, and the toluene layer is further washed with water until the water extract is just slightly alkaline. The toluene solution is then made acid with 6N hydrochloric acid and extracted with water until no cloudiness is produced when the extract is made alkaline. The acidic aqueous extract is washed with ether, then made alkaline with 20% sodium hydroxide solution, and extracted into ether. The ether solution is washed several times with water, then with saturated salt solution, and is dried over anhydrous potassium carbonate. The dried solution is filtered and distilled. The product distills at 143.5°C/1 mm; 69.7 g of pale yellow oil are recovered.

57.1 g of the free base are dissolved in ether and precipitated with dry HCl. 66.0 g of crude hydrochloride are recovered. The hydrochloride is dissolved in 130 ml of reagent acetone by boiling, filtered hot, and allowed to cool. The crystalline material obtained on cooling is filtered, washed with a little acetone, washed with ether, and dried in vacuo. 44.8 g, MP 119.5°C to 121°C, are recovered from the first crop of crystals. Ethyl acetate may also be used as the solvent for recrystallization.

**References**

Merck Index 7197
Kleeman & Engel p. 721
PDR p. 1606
OCDS Vol. 1 p. 115 (1977)
I.N. p. 766
Binkley, S.B. and Cheney, L.C.; U.S. Patent 2,703,324; March 1, 1955; assigned to Bristol Laboratories, Inc.

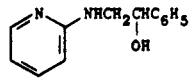
# PHENYRAMIDOL

**Therapeutic Function:** Analgesic, skeletal muscle relaxant

**Chemical Name:** α-[(2-Pyridinylamino)methyl] benzenemethanol

**Common Name:** Fenyramidol

**Structural Formula:**



**Chemical Abstracts Registry No.:** 553-69-5; 326-43-2 (Hydrochloride)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Analexin | Mallinckrodt | U.S. | 1960 |
| Cabral | Kali-Chemie | W. Germany | 1962 |
| Fenprin | RBS | Italy | 1962 |
| Anabloc | Irbi | Italy | — |
| Aramidol | A.B.C. | Italy | — |
| Bonapar | Minerva-Chemie | Neth. | — |
| Evasprine | Millot | France | — |
| Firmalgil | Firma | Italy | — |
| Miodar | I.S.M. | Italy | — |
| Pheniramidol | Pulitzer | Italy | — |
| Vilexin | Vitrum | Sweden | — |

**Raw Materials**

2-Aminopyridine
Lithium amide
Styrene oxide

**Manufacturing Process**

A mixture containing 18.8 g (0.20 mol) of 2-aminopyridine, 0.55 g of lithium amide and 75 cc of anhydrous toluene was refluxed for 1.5 hours. Styrene oxide (12.0 g = 0.10 mol) was then added to the reaction mixture with stirring over a period of ten minutes. The reaction mixture was stirred and refluxed for an additional 3.5 hours. A crystalline precipitate was formed during the reaction which was removed by filtration, MP 170°C to 171°C, 1.5 g. The filtrate was concentrated to dryness and a dark residue remained which was crystallized from anhydrous ether; yield 6.0 g. Upon recrystallization of the crude solid from 30 cc of isopropyl alcohol, 2.0 g of a light yellow solid was isolated; MP 170°C to 171°C.

**References**

Merck Index 7203
Kleeman & Engel p. 399
OCDS Vol. 1 p. 165 (1977)
I.N. p. 422
Biel, J.H.; U.S. Patent 3,040,050; June 19, 1962; assigned to Lakeside Laboratories, Inc.

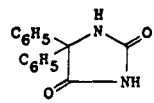
## PHENYTOIN

**Therapeutic Function:** Antiepileptic

**Chemical Name:** 5,5-diphenyl-2,4-imidazolidinedione

**Common Name:** Diphenylhydantoin

**Structural Formula:**




**Chemical Abstracts Registry No.:** 57-41-0

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Dilantin | Parke Davis | U.S. | 1938 |
| Ditan | Mallard | U.S. | 1980 |
| Aleviatin | Dainippon | Japan | – |
| Citrullamon | Sudmedica | W. Germany | – |
| Didan | Canfield | U.S. | – |
| Difhydan | Leo | Sweden | – |
| Dihydan | Carrion | France | – |
| Dihydantoin | Orion | Finland | – |
| Dintoina | Recordati | Italy | – |
| Diphentyn | I.C.N. | Canada | – |
| Enkefal | Leiras | Turkey | – |
| Epanutin | Parke Davis | W. Germany | – |
| Epinat | Nyegaard | Norway | – |
| Fenantoin | A.C.O. | Sweden | – |
| Hydantin | Medica | Finland | – |
| Hydantol | Fujinaga | Japan | – |
| Lehydan | Leo | Sweden | – |
| Novophenytoin | Novopharm | Canada | – |
| Phenhydan | Desitin | W. Germany | – |
| Pyoredol | Roussel | France | – |
| Solantyl | Roussel | France | – |
| Tacosal | Helvepharm | Switz. | – |
| Zentropil | Nordmark | W. Germany | – |

**Raw Materials**

Benzophenone
Potassium cyanide
Ammonium carbonate

**Manufacturing Process**

10 g of benzophenone (1 mol), 4 g of potassium cyanide (1.22 mols) and 16 g of ammonium carbonate (3.3 mols) are dissolved in 100 cc of 60% (by volume) ethyl alcohol and the mixture warmed under a reflux condenser without stirring at 58° to 62°C. After warming the mixture for 10 hours a partial vacuum is applied and the temperature is raised enough to permit concentration of the reaction mixture to two-thirds of its initial volume.

A slight excess of mineral acid, such as sulfuric or hydrochloric acid is added to acidify the mixture which is then chilled and the solid which separates is filtered off. It is then treated with an aqueous solution of dilute sodium hydroxide to dissolve the hydantoin from the solid unreacted benzophenone. After filtration, the alkaline extract is then acidified to cause the separation of solid pure diphenylhydantoin which is filtered off and dried. It melts at 293° to 296°C.

A net yield of about 95% is obtained by the procedure described above. If the time of warming the reaction mixture is increased three- or four-fold, practically 100% net yields are obtained. The same high net yields are also obtained by heating for even longer periods of time. For example, by heating for 90 hours, a 100% net yield, or 67% gross yield, is obtained.

**References**

Merck Index 7204
Kleeman & Engel p. 722
PDR pp. 1334, 1337
DOT 9 (6) 245 (1973)
I.N. p. 767

REM p. 1081
Henze, H.R.; U.S. Patent 2,409,754; October 22, 1946; assigned to Parke, Davis & Company

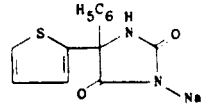
# PHETHENYLATE SODIUM

**Therapeutic Function:** Anticonvulsant

**Chemical Name:** 5-Phenyl-5-(2-thienyl)-2,4-imidazolidinedione monosodium salt

**Common Name:** –

**Structural Formula:**




**Chemical Abstracts Registry No.:** 510-34-9

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Thiantoin | Lilly | U.S. | 1950 |

**Raw Materials**

Phenyl-(2-thienyl)ketone
Potassium cyanide
Ammonium carbonate

**Manufacturing Process**

The 5-phenyl-5-(2-thienyl)hydantoin is prepared by heating a mixture of 5.64 g (0.03 mol) of phenyl-(2-thienyl)ketone, 3.25 g (0.03 mol) of potassium cyanide and 10.2 g (0.09 mol) of ammonium carbonate in 75 cc of 50% ethanol for 28 hours at a temperature of about 110°C. An additional 3.25 g of potassium cyanide and 3 g of ammonium carbonate are added and the mixture heated for 24 hours at about 110°C.

The reaction mixture is removed and about half of the liquid evaporated, an oil separating during the process. The mixture is acidified with concentrated hydrochloric acid and extracted with two 100 cc portions of ether. The extracts, which contain the 5-phenyl-5-(2-thienyl)hydantoin, are combined and the combined ether extracts are shaken with two 25 cc portions of 5% potassium hydroxide solution. The alkaline solution, which dissolves the 5-phenyl-5-(2-thienyl)hydantoin to form the potassium salt thereof, is acidifed with hydrochloric acid and heated to expel ether.

By the process of purification, 4.3 g of 5-phenyl-5-(2-thienyl)hydantoin is obtained, and from the ether layer, 2.2 g of unreacted ketone. The yield of the 5-phenyl-5-(2-thienyl)hydantoin is about 56%. The melting point of the purified 5-phenyl-5-(2-thienyl)hydantoin is about 256°C to 257°C.

**References**

Merck Index 7206
Spurlock, J.J.; U.S. Patent 2,366,221; January 2, 1945

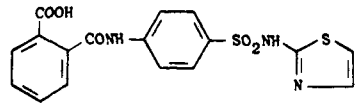
# PHTHALYLSULFATHIAZOLE

**Therapeutic Function:** Antibacterial (intestinal)

**Chemical Name:** 2-[[[4-[(2-thiazolylamino)sulfonyl] phenyl] amino] carbonyl] benzoic acid

**Common Name:** —

**Structural Formula:**




**Chemical Abstracts Registry No.:** 85-73-4

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Sulfathalidine | MSD | U.S. | 1946 |
| Talidine | Clin Midy | France | 1948 |
| AFI-Ftalyl | A.F.I. | Norway | — |
| Colicitina | Panthox & Burck | Italy | — |
| Enterosteril | Ripari-Gero | Italy | — |
| Ftalysept | Ferrosan | Denmark | — |
| Gelotamide | Choay | France | — |
| Lyantil | Syntex-Daltan | France | — |
| Novosulfina | Medosan | Italy | — |
| Phtalazol | Geistlich | Switz. | — |
| Phthalazol | Knoll | Australia | — |
| Sulfatalyl | Pharmacia | Sweden | — |
| Talisulfazol | Chemiek | E. Germany | — |
| Thalazole | May & Baker | U.K. | — |

**Raw Materials**

Phthalic anhydride
Sulfathiazole

**Manufacturing Process**

5 g of phthalic anhydride was added to a boiling suspension of 10 g of sulfathiazole in 100 cc of alcohol. The mixture was then refluxed for 5 minutes after the addition was complete at which time all of the solids were in solution. The solution was then cooled and diluted with an equal volume of water. The white solid precipitate which formed was filtered and recrystallized from dilute alcohol, yielding 2-$N^4$-phthalylsulfanilamidothiazole, which decomposes above 260°C, according to U.S. Patent 2,324,015.

**References**

Merck Index 7261
Kleeman & Engel p. 723
OCDS Vol. 1 p. 132 (1977)
I.N. p. 769
Moore, M.L.; U.S. Patent 2,324,013; July 13, 1943; assigned to Sharp & Dohme, Incorporated
Moore, M.L.; U.S. Patent 2,324,014; July 13, 1943; assigned to Sharp & Dohme, Incorporated
Moore, M.L.; U.S. Patent 2,324,015; July 13, 1943; assigned to Sharp & Dohme, Incorporated