X

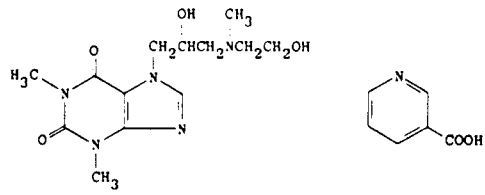
XANTHINOL NIACINATE

Therapeutic Function: Peripheral vasodilator

Chemical Name: 3-Pyridine carboxylic acid compounded with 3,7-dihydro-7-[2-hydroxy-3-[(2-hydroxymethyl)methylamino] propyl] -1,3-dimethyl-1H-purine-2,6-dione(1:1)

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 437-74-1

Trade Name	Manufacturer	Country	Year Introduced
Complamex	Calder	U.K.	1971
Adrogeron	Adroka	Switz.	–
Angioamin	Dompe	Italy	–
Circulan	Unipharm	Israel	–
Complamin	Riker	U.S.	–
Digi-Complamin	Beecham-Wulfing	W. Germany	–
Emodinamin	Sigurta	Italy	–
Jupal	Arzneimittelwerk Dresden	E. Germany	–
Landrina	Landerlan	Spain	–
Niconicol	Farmos	Finland	–
Retilian	Kwizda	Austria	–
Sadamin	Polfa	Poland	–
Teonicol	Farmos	Finland	–
Vasoprin	Alfa	Italy	–
Vedrin	Polifarma	Italy	–
Xanidil	Spofa	Czechoslovakia	–
Xavin	Chinoin	Hungary	–

Raw Materials

Epichlorohydrin
Methylaminoethanol
Theophylline
Nicotinic acid

Manufacturing Process

To a well-stirred solution of 740 parts by weight of epichlorohydrin in 200 parts by volume of isopropyl alcohol are added 600 parts by weight of methylaminoethanol during about 3

hours at 15°C to 20°C. The heat generated by the condensation is removed by means of a cooling bath. After the addition of the total quantity of methylaminoethanol, stirring is continued for 1 hour at 25°C. The condensation reaction is completed when development of heat reaction can no longer be observed. The solution thus produced of the raw 1-chloro-3-(methylhydroxyethylamino)-propanol-2 in isopropyl alcohol is a colorless viscous liquid which is used without further purification for the subsequent condensation with theophylline.

320 parts by weight of caustic soda are dissolved in 200 parts by weight of water and diluted with 6,000 parts by weight of isopropyl alcohol. 1,584 parts by weight of theophylline-hydrate are added to the well-stirred alcoholic caustic soda solution having a temperature between 50°C to 60°C. As a result, most of the theophylline sodium salt is precipitated and a doughy or pasty white reaction product is formed. While being stirred and heated to the boiling point of alcohol, the solution of the afore-described 1-chloro-3-(methylhydroxyethylamino)-propanol-2 is added dropwise into the reaction vessel during about 3 hours. After further cooking for 2 hours, the alcoholic solution of deposited sodium chloride is filtered off. By vaporizing the alcohol, the 3-(methylhydroxyethylamino)-2-hydroxypropyltheophylline can be obtained as a very viscous oil which contains impurities in the form of by-products.

For purpose of purification, the hot alcoholic solution is mixed with 975 parts by weight of nicotinic acid while being stirred and heated until the nicotinic acid is completely dissolved.

The 3-(methylhydroxyethylamino)-2-hydroxypropyltheophylline-nicotinate separates, while still being warm, in the form of shiny, thin, small sheets. After cooling, the crystallization product is sucked off from the mother liquor and recrystallized from 85% isopropyl alcohol.

The melting point of the pure nicotinic acid salt is 180°C and the yield is 75% to 80% related to the used theophylline. The substance has a nearly neutral reaction and is very readily soluble in water.

References

Merck Index 9871
Kleeman & Engel p. 951
I.N. p. 1018
Bestian, A.H.W.; U.S. Patent 2,924,598; February 9, 1960; assigned to Firma Johann A. Wulfing (Germany)

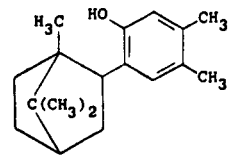
XIBORNOL

Therapeutic Function: Antibacterial

Chemical Name: 6-Isobornyl-3,4-xylenol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 13741-18-9

Trade Name	Manufacturer	Country	Year Introduced
Nanbacine	Fournier	France	1976
Xibol	Reig Jofre	Spain	–

Raw Materials

3,4-Xylenol
Camphene

Manufacturing Process

100 g of 3,4-xylenol and 150 g of camphene are melted in a two-necked flask equipped with a reflux condenser and a thermometer. 10 g of stannic chloride are added in small quantities; the temperature is kept between 70°C and 80°C for 4 hours. The mass is then allowed to cool and 300 ml of benzene and 300 ml of water are added. The aqueous layer is decanted off, and the supernatant organic layer is washed, first with 1,200 ml of 10% potassium hydroxide and then with water until neutral. The benzene is driven off and the mass is distilled. The fraction which passes between 203°C and 223°C/200 mm Hg is collected and recrystallized in petroleum ether.

100 mg of the recrystallized product is dissolved in 10 ml of hexane.

This solution is then slowly passed through a chromatographic alumina column, 20 cm in length and 16 mm in diameter, containing 20 g of alumina (Prolabo®).

The column is then eluted with benzene and 2 ml fractions of the eluent are collected as soon as the product appears in the eluent. The presence of the product is detected by means of the color change in the collected eluent after adding 1 drop of 2% ferric chloride and 2 drops of 5% potassium ferricyanide solution.

18 ml of a first fraction are collected, the next 2 ml of eluent are discarded and then a second fraction of 20 ml is collected. Removal of the solvent from the first fraction by distillation leaves a product having a melting point of between 94°C and 96°C and removal of the solvent from the second fraction leaves a product having a melting point between 86°C and 88°C.

The product remaining from the first fraction is 6-isobornyl-3,4-xylenol while that from the second fraction is its isomer 6-exo-isocamphenyl-3,4-xylenol.

References

Merck Index 9887
Kleeman & Engel p. 952
DOT 8 (6) 235 (1972)
I.N. p. 1019
Mar-Pha, Societe d'Etude et d'Exploitation de Marques; British Patent 1,206,774; Sept. 30, 1970

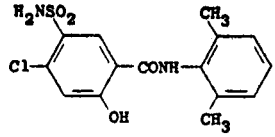
XIPAMID

Therapeutic Function: Diuretic; antihypertensive

Chemical Name: 4-chloro-5-sulfamoyl-2',6'-salicyloxylidide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 14293-44-8

Trade Name	Manufacturer	Country	Year Introduced
Aquaphor	Beiersdorf	W. Germany	1971
Diurexan	Merck	U.K.	1979
Aquaphor	Farmades	Italy	1980
Aquaphoril	Homburg	W. Germany	–
Diurex	Lacer	Spain	–

Raw Materials

4-Chlorosalicylic acid
Ammonia
Phosphorus trichloride
Chlorosulfonic acid
2,6-Dimethylaniline

Manufacturing Process

The 4-chloro-5-sulfamyl salicylic acid used as starting point was prepared in the following way:

(a) 4-Chloro-5-Chlorosulfonyl Salicylic Acid: 100 grams 4-chloro salicylic acid was added portionwise with stirring at about -5°C to 275 ml chlorosulfonic acid. The temperature was not allowed to rise above +3°C. At the end of the addition, the solution formed was stirred for 1 hour in an ice bath, then for 1 hour at 20°C and finally for 2½ hours at 80°C oil bath temperature. Then the dark brown solution, after ensuing slow cooling with vigorous stirring, was poured onto ice; the precipitate was vacuum filtered, washed with water and dried. After recrystallization from toluene the compound formed had a melting point of 181° to 183°C.

(b) 4-Chloro-5-Sulfamyl Salicylic Acid: 40 grams 4-chloro-5-chlorosulfonyl salicylic acid obtained from (a) was added portionwise with stirring to 250 ml liquid ammonia. This was allowed to stand for 2 hours, then the precipitate was vacuum filtered and dissolved in 500 ml water. The solution was filtered and the filtrate was treated with 2 N hydrochloric acid until no more precipitation occurred. The 4-chloro-5-sulfamyl salicylic acid obtained as the precipitate was filtered off and finally recrystallized from water, MP 258° to 260°C.

5.0 grams 4-chloro-5-sulfamyl salicylic acid was suspended in 100 ml water-free chlorobenzene and then 2.44 grams of 2,6-dimethylaniline and 0.9 ml phosphorus trichloride were added to the suspension in turn. The reaction mixture was heated under reflux for 5 hours. After cooling, the chlorobenzene was separated from the precipitate by decantation. The latter was finally collected on a filter and washed, first with chlorobenzene and, after drying, with 2 N hydrochloric acid and water. The compound obtained by recrystallization from methanol had a melting point of 256°C.

References

Merck Index 9888
Kleeman & Engel p. 952
OCDS Vol. 2 p. 93 (1980)
DOT 7 (6) 227 (1971)
I.N. p. 1019
Liebenow, W.; U.S. Patent 3,567,777; March 2, 1971; assigned to P. Beiersdorf & Co., AG, Germany

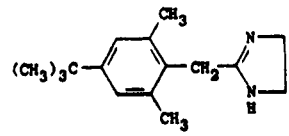
XYLOMETAZOLINE HYDROCHLORIDE

Therapeutic Function: Adrenergic (vasoconstrictor)

Chemical Name: 2-[[4-(1,1-Dimethylethyl)-2,6-dimethylphenyl] methyl] -4,5-dihydro-1H-imidazole hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1218-35-5; 526-36-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Otrivin	Geigy	U.S.	1959
Coryzin	Star	Finland	–
Hidropid	Pliva	Yugoslavia	–
Ilvanol	Siegfried	W. Germany	–
Novorin	Polfa	Poland	–
Olynth	Goedecke	W. Germany	–
Servilaryn	Servipharm	Switz.	–
Sinutab	Parke Davis	U.S.	–

Raw Materials

p-tert-Butyl-o,o'-dimethylphenylacetonitrile
Ethylenediamine
Hydrogen chloride

Manufacturing Process

62 grams of para-tertiary-butyl-ortho,ortho'-dimethyl-phenyl-acetonitrile [obtainable, for example, by the method of Buu-Hoi and P. Cagniant, *Bulletin de la Societe Chimique de France,* volume 9, page 891 (1942)], 20.6 grams of ethylenediamine of 96% purity and 1.55 cc of carbon disulfide are heated together in a distillation flask with the exclusion of moisture for 48 hours on a boiling water bath. Ammonia is evolved. Upon cooling the reaction product solidifies and is then dissolved in benzene, the solution is filtered while hot with the addition of animal charcoal and petroleum ether is added. The mixture is filtered to remove the impurities that are first precipitated and by the further addition of petroleum ether 2-(para-tertiary-butyl-ortho,ortho'-dimethyl-phenyl-methyl)-imidazoline is caused to crystallize out.

The product melts at 131° to 133°C after being recrystallized from a mixture of benzene and petroleum ether. It can be converted into its hydrochloride as follows:

189 grams of 2-(para-tertiary-butyl-ortho,ortho'-dimethyl-phenyl-methyl)-imidazoline are dissolved in 400 cc of absolute ethanol, the solution is rendered acid by the addition of 104 cc of an ethanolic solution of hydrochloric acid of 30% strength, the mixture is filtered with the addition of animal charcoal, and dry ethyl acetate and absolute ether are added until crystallization sets in. After cooling the mixture, the salt is filtered off with suction and crystallized several times from absolute ethanol with the use of animal charcoal and the addition of dry mixture of ethyl acetate and ether. The hydrochloride so obtained melts at 327° to 329°C (with decomposition).

References

Merck Index 9895
Kleeman & Engel p. 953
PDR p. 898
OCDS Vol. 1 p. 242 (1977)
I.N. p. 1020
REM p. 891
Hueni, A.; U.S. Patent 2,868,802; January 13, 1959; assigned to Ciba Pharmaceutical Products Inc.

Z

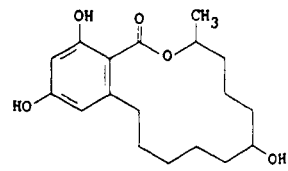
ZERANOL

Therapeutic Function: Estrogen

Chemical Name: 3,4,5,6,7,8,9,10,11,12-Decahydro-7,14,16-trihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1-one

Common Name: Zearalanol, tetrahydro F.E.S. (fermentation estrogenic substance)

Structural Formula:



Chemical Abstracts Registry No.: 26538-44-3

Trade Name	Manufacturer	Country	Year Introduced
Ralone	I.C.I.	Italy	1975
Frideron	Sandoz	Italy	–
Ralgro	Comm. Solvents	Italy	–

Raw Materials

Bacterium *Gibberella zeae*
Nutrient medium
Hydrogen

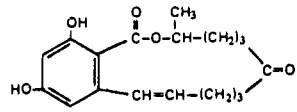
Manufacturing Process

A spore sand culture containing *Gibberella zeae* (Gordon) NRRL-2830 was aseptically placed in a sterile tube containing 15 ml of Czapek's-Dox solution and a small amount of agar. This medium was then incubated for about 168 hours at approximately 25°C. At the end of the incubation period, the medium was washed with 5 ml of sterile deionized water and transferred to a sterile tube containing 45 ml of Czapek's-Dox solution. The contents of the tube were then incubated for about 96 hours at about 25°C after which the material was available for use in inoculation of a fermentation medium.

To a 2-liter flask were added 300 g of finely divided corn. The flask and its contents were then sterilized and after sterilization 150 ml of sterile deionized water were added. To the mixture in the flask were then added 45 ml of the inoculum prepared by the process and the material was thoroughly mixed. The mixed material was then incubated for about 20 days at 25°C in a dark room in a water-saturated atmosphere. The following illustrates the recovery of the anabolic substance from the fermentation medium.

A 300-g portion of fermented material was placed in 500 ml of deionized water and slurried.

The slurry was then heated for about 15 minutes at 75°C, 300 g of filter aid were then added and the material was filtered. The solid filtered material containing the anabolic substance was then air dried, and 333 g of the dried cake were then extracted with 500 ml of ethanol. This procedure was repeated three more times. The ethanol extract was then dried under vacuum to give 6.84 g of solid material. This solid material was then dissolved in 20 ml of chloroform and extracted with 30 ml of an aqueous solution containing 5% by weight of sodium carbonate having an adjusted pH of about 11.2. The extraction process was repeated seven more times. The pH of the sodium carbonate extract was then adjusted to 6.2 with hydrochloric acid, to yield an anabolic substance-containing precipitate. The precipitate and the aqueous sodium carbonate extract were then each in turn extracted with 75 ml of ethyl ether. This procedure was repeated three more times to yield a light yellow ethereal solution, which was then dried to yield 116 mg of solid anabolic substance. This material was then subjected to multiple transfer countercurrent distribution using 100 tubes and a solvent system consisting of two parts chloroform and two parts methanol and one part water as the upper phase, all parts by volume. The solid material obtained from the multiple transfer countercurrent distribution was then tested for physiological activity according to the well-known mouse-uterine test. The fermentation estrogenic substance produced has the formula:



Tetrahydro F.E.S. was produced by dissolving 0.5 g F.E.S. in 200 ml of ethanol. The F.E.S. was reduced by contacting the solution with hydrogen for 3 hours at 30°C and 1,000 psi using 2 g of Raney nickel as a catalyst. After filtering and concentrating the reaction mixture, the product was washed with 2 to 3 ml of 2-nitropropane and crystallized. It was found to have a melting point from 143°C to 160°C.

References

Merck Index 9923
Kleeman & Engel p. 953
DOT 12 (6) 243 (1976)
I.N. p. 1023
Hodge, E.B., Hidy, P.H. and Wehrmeiser, H.L.; U.S. Patent 3,239,345; March 8, 1966; assigned to Commercial Solvents Corp.
Andrews, F.N. and Stob, M.; U.S. Patent 3,196,019; July 20, 1965; assigned to Purdue Research Foundation

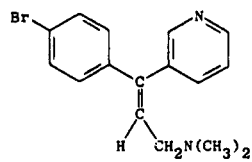
ZIMELIDINE

Therapeutic Function: Antidepressant

Chemical Name: 3-(4-Bromophenyl)-N,N-dimethyl-3-(3-pyridinyl)-2-propen-1-amine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 56775-88-3

Trade Name	Manufacturer	Country	Year Introduced
Normud	Astra	W. Germany	1981
Zelmid	Astra	U.K.	1982
Normud	Astra	Switz.	1982
Zelmid	Astra	Sweden	1983

Raw Materials

ω-Dimethylamino-4'-bromopropiophenone
3-Bromopyridine
n-Butyllithium
Sulfuric acid

Manufacturing Process

To 9 g of n-butyllithium in 200 ml of dry ether 20 g of 3-bromopyridine is added as quickly as possible at -40°C without raising the temperature. When the addition is finished the mixture is stirred for another 30 minutes. Thereafter 32.5 g of ω-dimethylamino-4'-bromopropiophenone is added in such a way that the temperature does not exceed -40°C. The cooling is discontinued and the mixture is stirred during the night whereupon the reaction mixture is poured onto ice and diluted HCl, which is washed with ether and is extracted with 20 ml of methylene dichloride. The methylene dichloride is dried and evaporated. The crystals are dissolved in water, which then is made alkaline with a solution of Na_2CO_3, is extracted with ether, dried, and evaporated and recrystallized from isopropyl ether, petroleum ether 1:1. Yield 4 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(3''-pyridyl)-propanol. Melting point 67°C.

3.6 g of 1-(4'-bromophenyl)-3 (N,N-dimethylamino)-1-(3''-pyridyl)-propanol are dissolved in 15 ml of 85% H_2SO_4 and heated at 170°C for 10 minutes. The reaction mixture is poured into 60 ml of water, which is then made alkaline with 10N NaOH, and is extracted with 2 X 25 ml of ether. The ether is dried with Na_2SO_4, treated with active carbon and evaporated. The residue is dissolved in 25 ml of acetone and an equivalent amount of oxalic acid dissolved in 25 ml of acetone is added. The precipitate obtained is filtered off, is dissolved in 50 ml of water, which is made alkaline with 10N NaOH and is extracted with 2 X 25 ml of ether. The ether solution is dried with Na_2SO_4 and is filtered, whereupon dry HCl is introduced. The precipitate obtained is filtered off. Yield 1.2 g of 3-(4'-bromophenyl)-3-(3''-pyridyl)-dimethylallylamine dihydrochloride (H 102/09). Melting point 193°C.

References

Merck Index 9924
DFU 3 (1) 71 (1978)
OCDS Vol. 3 p. 49 (1984)
DOT 18 (9) 449 (1982)
I.N. p. 1023
Berntsson, P.B., Carlsson, P.A.E. and Corrodi, H.R.; U.S. Patent 3,928,369; December 23, 1975; assigned to A.B. Hassle (Sweden)

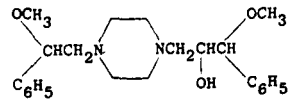
ZIPEPROL

Therapeutic Function: Bronchodilator

Chemical Name: 4-(2-methoxy-2-phenylethyl)-α-(methoxyphenylmethyl)-1-piperazine-ethanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 34758-83-3; 34758-84-4 (Dihydrochloride).

Trade Name	Manufacturer	Country	Year Introduced
Respilene	Winthrop	France	1973
Respilene	Sigma Tau	Italy	1979
Antituxil	Ghimas	Italy	–
Bronx	Lisapharma	Italy	–
Citizeta	C.T.	Italy	–
Mirsol	Mepha	Switz.	–
Respirase	Gibipharma	Italy	–
Respirex	Inibsa	Spain	–
Sanotus	Krka	Yugoslavia	–
Talasa	Andromaco	Argentina	–
Zitoxil	Farmochimica	Italy	–

Raw Materials

1-(2-Phenyl-2-methoxy)ethyl piperazine
3-Phenyl-3-methoxy propylene oxide

Manufacturing Process

In a reactor provided with a mechanical stirrer, a reflux refrigerant and a thermometer, there is introduced: 393 grams 1-[2-phenyl, 2-methoxy] ethyl piperazine and 22 grams 3-phenyl-3-methoxy propylene oxide in 750 ml of absolute ethanol.

When the slightly exothermic reaction (rise in temperature of about 20°C) has ceased, heating is effected for 1.5 hours at 60°C. The product is then cooled to 4°C and left to crystallize for about 12 hours. The precipitate is centrifugated then recrystallized in 500 ml of absolute ethanol.

420 grams of the desired compound is thus obtained in the form of a white, crystalline powder, melting point 83°C.

References

Merck Index 9976
Kleeman & Engel p. 953
DOT 10 (3) 104 (1974)
I.N. p. 1024
Mauvernay, R.Y., Busch, N., Moleyre, J. and Simond, J.; U.S. Patent 3,718,650; February 27, 1973; assigned to Societe Anonyme Centre Europeen de Recherches Mauvernay, France

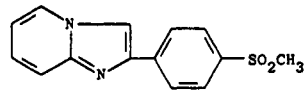
ZOLIMIDINE

Therapeutic Function: Antiulcerative

Chemical Name: 2-[4-(Methylsulfonyl)phenyl] imidazo[1,2-a] pyridine

Common Name: Zoliridine

Structural Formula:



Chemical Abstracts Registry No.: 1222-57-7

Trade Name	Manufacturer	Country	Year Introduced
Solimidin	Selvi	Italy	1974
Gastronilo	Aristegui	Spain	–
Mutil	Lakeside	U.S.	–

Raw Materials

2-Aminopyridine
p-Methylsulfonyl-ω-bromoacetophenone

Manufacturing Process

190 g of 2-aminopyridine were dissolved in 350 ml of dioxane and the solution was reacted with 277 g of p-methylsulfonyl-ω-bromoacetophenone. After two hours at room temperature the 2-(4'-methylsulfonylphenyl) [1,2-a] imidazopyridine was filtered, washed and recrystallized by alcohol.

References

Merck Index 9992
Kleeman & Engel p. 954
DOT 10 (6) 210 (1974)
I.N. p. 1024
Almirante, L., Murmann, W. and Friz, L.P.; U.S. Patent 3,318,880; May 9, 1967; assigned to Laboratorio Bioterapico Milanese Selvi & Co. S.a.S. (Italy)

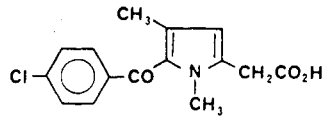
ZOMEPIRAC

Therapeutic Function: Analgesic, antiinflammatory

Chemical Name: 5-(p-Chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 33369-31-2

Trade Name	Manufacturer	Country	Year Introduced
Zomex	Cilag	Switz.	1979
Zomax	McNeil	U.S.	1980

Trade Name	Manufacturer	Country	Year Introduced
Zomax	Cilag	France	1981
Zomax	Cilag	W. Germany	1981
Zomax	Ortho	U.K.	1981
Zomaxin	Cilag	Italy	1982
Calmador	Finadiet	Argentina	–
Dolgenal	Exa	Argentina	–
Dolwas	Wassermann	Spain	–
Zopirac	Sintyal	Argentina	–

Raw Materials

Ethyl 5-(p-chlorobenzoyl)-1,4-dimethyl-3-ethoxypyrrole-2-acetate
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

5-(p-Chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetic acid: A suspension of 17.3 g (0.0435 mol) of ethyl 5-(p-chlorobenzoyl)-1,4-dimethyl-3-ethoxypyrrole-2-acetate in 170 g of 25% hydroxide is heated under reflux for 3 hours. The suspension is poured into ice and the resulting yellow solution is added to ice-hydrochloric acid with stirring. The precipitated solid is collected by filtration, air dried and recrystallized from acetone containing 10% water to give 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetic acid as a white solid; melting point 253°C to 254°C.

Ethyl 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetate: A suspension of 2.0 g of 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetic acid in 20 ml of 0.5% ethanolic hydrogen chloride is heated under reflux. The solid gradually dissolves. After 40 minutes a white crystalline solid precipitates. The solution is cooled and the solid product, ethyl 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetate, is filtered and dried, melting point 197°C to 198°C.

Ethyl 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetate: A 9.0 g (0.0255 mol) sample of ethyl 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetate is heated under nitrogen at 210°C to 230°C for 2 hours. Gas is evolved. The residue is molecularly distilled in a sublimator at 195°C, 0.05 mm/Hg. The sublimate is recrystallized from cyclohexane to give ethyl 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetate as a white solid, melting point 107°C to 109°C.

5-(p-Chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid: A suspension of 4.0 g (0.0125 mol) of ethyl 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetate in 26 ml of 0.5 N sodium hydroxide (0.013 mol) is heated under reflux for 30 minutes. The resulting solution is acidified with dilute hydrochloric acid, and the precipitated solid is collected by filtration, air dried and recrystallized from 2-propanol to give 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid as a white crystalline solid, melting point 178°C to 179°C.

References

Merck Index 9993
DFU 2 (10) 698 (1977)
Kleeman & Engel p. 955
OCDS Vol. 3 p. 128 (1984)
DOT 16 (12) 434 (1980)
I.N. p. 1025
Carson, J.R.; U.S. Patents 3,752,826; August 14, 1973 and 3,865,840; February 11, 1975; both assigned to McNeil Laboratories, Inc.

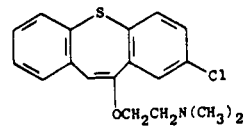
ZOTEPINE

Therapeutic Function: Tranquilizer (major)

Chemical Name: 2-[(8-Chlorodibenzo[b,f] thiepin-10-yl)oxy] -N,N-dimethylethanamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 26615-21-4

Trade Name	Manufacturer	Country	Year Introduced
Lodopin	Fujisawa	Japan	1982

Raw Materials

8-Chlorodibenzo[b,f] thiepin-10(11H)one
2-Dimethylaminoethyl chloride

Manufacturing Process

A suspension of 30 g of sodium hydride in benzene (30 ml) was added dropwise to 52 g of 8-chlorodibenzo[b,f] thiepin-10(11H)-one dissolved in dimethylformamide (800 ml), and the mixture was heated at 100°C for 2 hours. To this, there were added 68 g of 2-dimethylaminoethyl chloride, and the mixture was heated at 60°C for 39 hours. The reaction mixture, after cooled, was poured into ice-water, and the solution was extracted with ethyl acetate. The ethyl acetate layer, after washed with water, was extracted with 10% hydrochloric acid, when oil was precipitated. The aqueous layer, in which oil was precipitated, was washed with ether, made neutral with concentrated sodium hydroxide solution and then extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over magnesium sulfate, and concentrated to give oil, which was allowed to stand to provide solid. The solid was washed with petroleum ether and recrystallized from cyclohexane to yield 42.5 g of 8-chloro-10-(2-dimethylaminoethyl)-oxydibenzo[b,f] thiepin as crystals, melting point 90°C to 91°C. Maleate as colorless needle, melting point 204°C to 204.5°C.

References

Merck Index 9997
DOT 19 (3) 155 (1983)
I.N. p. 1025
Umio, S., Uedo, I., Sato, Y. and Maeno, S.; U.S. Patent 3,704,245; November 28, 1972

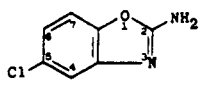
ZOXAZOLAMINE

Therapeutic Function: Skeletal muscle relaxant; uricosuric

Chemical Name: 5-Chloro-2-benzoxazolamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: —

Trade Name	Manufacturer	Country	Year Introduced
Flexin	McNeil	U.S.	1956
Contrazole	Millot	France	—
Deflexol	Millot	France	—
Zoxine	Millot	France	—

Raw Materials

2-Amino-4-chlorophenol
Hydrogen chloride
Ammonium hydroxide
Ammonium thiocyanate
Ferric chloride

Manufacturing Process

To a solution of 106 g (0.74 mol) of 2-amino-4-chlorophenol in 500 ml of water containing 69 ml of concentrated hydrochloric acid (29.2 g, 0.8 mol) are added 60.8 g (0.8 mol) of ammonium thiocyanate. The solution is placed in an evaporating dish and heated on a steam bath for 5 hours. The solid which results is then removed from the concentrated solution by filtration, washed with a small amount of water and dried. The filtrate is placed in an evaporating dish and heated on a water bath for 2 hours. At the end of this time, the mixture is cooled, and the solid which precipitates out is removed by filtration. Both solid products are 5-chloro-2-hydroxyphenylthiourea melting at 157°C, and may be combined. The calculated N content for $C_7H_7ClN_2OS$ is 13.8; that found is 13.6.

To a solution of 10 g (0.05 mol) of 2-hydroxy-5-chlorophenylthiourea in 50 ml of methanol is added a solution of 11 g (0.04 mol) of ferric chloride hexahydrate in 50 ml of methanol. The initial purple-red color changes in a few minutes to amber. After stirring for one-half hour, the solution is treated with 16.5 ml of 57% ammonium hydroxide solution (0.24 mol). A brown, flocculent precipitate of ferric sulfide appears. The mixture is then refluxed with stirring for one hour, cooled and centrifuged. The centrifugate is evaporated to dryness, and the residue is shaken with ether and water to separate the organic material from the ammonium chloride. The ether layer is extracted three times with 25 ml portions of 1 N hydrochloric acid. The acid solution is then poured into excess ammonium hydroxide, and the resulting solid collected, washed with water and dried. This gives a light tan solid melting at 183°C to 185°C. The material is then dissolved in 25 ml of acetone and 50 ml of benzene are added. After treatment of the solution with activated charcoal, the light yellow solution is evaporated to 25 ml and cooled. The white crystals of 2-amino-5-chlorobenzoxazole which separate melt at 185°C to 186°C.

References

Merck Index 9998
I.N. p. 1025
Sam, J.; U.S. Patent 2,780,633; February 5, 1957; assigned to McNeil Laboratories, Inc.