F

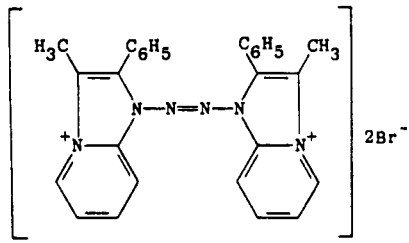
FAZIDINIUM BROMIDE

Therapeutic Function: Skeletal muscle relaxant

Chemical Name: 1,1'-Azobis[3-methyl-2-phenylimidazo[1,2-a] pyridinium] dibromide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 49564-56-9

Trade Name	Manufacturer	Country	Year Introduced
Fazadon	Duncan Flockhart	U.K.	1976
Fazadon	Glaxo	Italy	1981

Raw Materials

2-(2-Acetylhydrazino)pyridine
2-Bromopropiophenone
Hydrogen bromide
Bromine

Manufacturing Process

(a) 1-Acetamido-3-methyl-2-phenylimidazo[1,2-a] pyridinium bromide—A mixture of 2-(2-acetylhydrazino)pyridine (2 g) and 2-bromopropiophenone (2.84 g), in ethanol (10 ml) was heated in an open flask in a bath at 160°C to 170°C until the ethanol had evaporated; the residual melt was then heated for a further 0.25 hour. After cooling, the residual gum was triturated with acetone and the resulting solid (2.8 g) recrystallized from ethanol-ether giving the *bromide* as colorless prisms, MP 232°C to 234°C.

(b) 1-Amino-3-methyl-2-phenylimidazo[1,2-a] pyridinium bromide—A solution of the acetamido compound (2.78 g) in 24% hydrobromic acid (12 ml) was boiled under reflux for 1 hour. The solution was then evaporated under reduced pressure and the residue dissolved in methanol. Addition of ether precipitated the *bromide* which crystallized from ethanol as colorless prisms, MP 243°C to 244°C (1.7 g).

(c) 1,1'-Azobis[3-methyl-2-phenyl-1H-imidazo[1,2-a] pyridinium] dibromide—A warm (50°C) solution of the N-amino compound (0.6 g) in water (10 ml) was treated with saturated bro-

mine water (70 ml) and the precipitated orange solid filtered off and washed with water. The orange solid was sucked dry and then boiled with acetone (30 ml) until the suspended solid became yellow. Absolute acetone (10 ml) was then added and the solution filtered giving the *dibromide* (0.57 g) which crystallized from water as the yellow dihydrate, MP 215°C to 219°C (softened at 196°C).

References

Merck Index 3878
DFU 1 (10) 466 (1976)
DOT 13 (3) 98 (1977)
I.N. p. 413
Jack, D. and Glover, E.E.; U.S. Patents 3,773,746; November 20, 1973 and 3,849,557; November 19, 1974; both assigned to Allen & Hansburys Ltd.

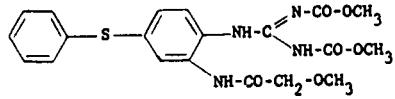
FEBANTEL

Therapeutic Function: Anthelmintic

Chemical Name: Dimethyl[[2-(2-methoxyacetamido)-4-phenylthiophenyl]-imidacarbonyl]-dicarbamate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 58306-30-2

Trade Name	Manufacturer	Country	Year Introduced
Rintal	Bayer	W. Germany	1979

Raw Materials

2-Amino-5-phenylthiomethoxyacetanilide
N,N'-Bis-methoxycarbonylisothiourea-S-methyl ether

Manufacturing Process

2-Amino-5-phenylthiomethoxyacetanilide in methanol solution is heated with N,N'-bis-methoxycarbonyl-isothiourea-S-methyl ether with the addition of a catalytic amount of p-toluenesulfonic acid for three hours with stirring under reflux. The mixture is then filtered hot and after cooling the febantel product crystallizes out. It is filtered off, rinsed with ether and dried under high vacuum to give the final product, melting at 129°C to 130°C.

References

Merck Index 3879
DFU 3 (5) 377 (1978)
I.N. p. 413
Kolling, H., Thomas, H., Widdig, A. and Wollweber, H.; U.S. Patent 4,088,780; May 9, 1978; assigned to Bayer AG

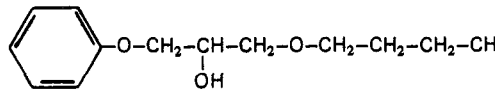
FEBUPROL

Therapeutic Function: Choleretic agent

Chemical Name: 3-n-Butoxy-1-phenoxy-2-propanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3102-00-9

Trade Name	Manufacturer	Country	Year Introduced
Valbil	Rohm Pharma	W. Germany	1981
Valbil	Klinge	W. Germany	–

Raw Materials

n-Butylglycidyl ether
Phenol
Potassium hydroxide

Manufacturing Process

Initially, 4.5 g (0.08 mol) pulverized potassium hydroxide was dissolved in 300 ml isopropanol in a 500 ml four-neck flask equipped with stirrer, intensive cooler, dropping funnel and feed pipe for the gas treatment with nitrogen.

Then, 52.0 g (0.4 mol) n-butylglycidyl ether and 41.4 g (0.44 mol) phenol was added thereto, whereafter the material was heated to boiling under nitrogen. The material was stirred, about 8.5 hours, until no glycidyl ether could be determined, e.g., by gas chromatography.

After the suspension was cooled under nitrogen, the solvent was distilled off under vacuum. The residue was taken up in 200 ml water and the milky emulsion extracted exhaustively with ether. From the organic phase, the excess butylglycidyl ether was extracted with diluted potassium hydroxide solution. The ether phase was washed neutral with water and the solvent removed after drying with sodium sulfate. The remaining oily residue was distilled under vacuum; there was obtained a colorless liquid of BP 123.5°C/0.07 mm. Yield: 81.8 g (91.1% of the theory).

References

Merck Index 3882
DFU 3 (3) 191 (1978)
DOT 19 (12) 683 (1983)
I.N. p. 413
Hoffmann, H., Wagner, J., Hofrichter, G. and Grill, H.; U.S. Patent 3,839,587; October 1, 1974; assigned to Chemisch-Pharmazeutische Fabrik Adolf Klinge and Co.

FELYPRESSIN

Therapeutic Function: Vasoconstrictor

Chemical Name: Vasopressin 2-(L-phenylalanine)-8-L-lysine

Common Name: –

Structural Formula: Cys-Phe-Phe-Gln-Asn-Cys-Pro-Lys-GlyNH_2

Chemical Abstracts Registry No.: 56-59-7

Trade Name	Manufacturer	Country	Year Introduced
Octapressin	Sandoz	W. Germany	1967
Octapressin	Sandoz	Japan	1971
Colupressine	Joullie	France	–

Raw Materials

N-Carbobenzoxy-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide
N-Carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-azide
N-Carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl azide
Oxygen
Ammonia
Acetic acid
Hydrogen bromide

Manufacturing Process

Preparation of N-Carbobenzoxy-L-Glutaminyl-L-Asparaginyl-S-Benzyl-L-Cysteinyl-L-Prolyl-ε-N-p-Toluenesulfonyl-L-Lysylglycinamide: 200 parts by weight of N-carbobenzoxy-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide are dissolved in 1,000 parts by volume of anhydrous acetic acid which has been saturated with HBr, the mixture allowed to stand for 1 hour at 20°C and then evaporated under reduced pressure at below 40°C. The residue from this evaporation is carefully washed with diethyl ether and then added to a solution of 185 parts by weight of N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-azide and 48 parts by volume of triethylamine in 1,500 parts by volume of dimethylformamide. The mixture is allowed to stand overnight at 20°C and the mixture is then poured into twice its volume of acetone. The precipitate which settles out is filtered off, washed with water, and recrystallized from dimethylformamide-acetone. There are thus obtained 190 parts by weight of N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide; MP 165°C (decomposition).

Preparation of N-Carbobenzoxy-S-Benzyl-L-Cysteinyl-L-Phenylalanyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-S-Benzyl-L-Cysteinyl-L-Prolyl-ε-N-p-Toluenesulfonyl-L-Lysyl-Glycinamide: 50 parts by weight of N-carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide are dissolved in 400 parts by volume of anhydrous acetic acid which is saturated with HBr, and the mixture allowed to stand for 1 hour at 20°C. After evaporating off the solvent under reduced pressure at a temperature of 35°C (or another temperature below 40°C), the residue is carefully washed with diethyl ester, whereupon a solution of 32 parts by weight of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl-L-phenylalanyl-azide and 70 parts by volume of triethylamine in 500 parts by volume of dimethylformamide is added.

The mixture is allowed to stand for 2 days at 20°C, after which twice its volume of ethyl-acetate is added and the resultant precipitate then washed with warm methanol. There are obtained 45 parts by weight of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide; MP 222°C.

Preparation of L-Cysteinyl-L-Phenylalanyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-

Cysteinyl-L-Prolyl-L-Lysyl-Glycinamide: Metallic potassium is stirred into a solution of 10 parts by weight of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-ε-N-p-toluenesulfonyl-L-lysyl-glycinamide in 2,500 parts of dry liquid ammonia at boiling temperature of the solution, until a stable blue coloration appears. After the addition of 1.8 parts by weight of ammonium chloride, the solution is evaporated to dryness. The residue of this evaporation contains the desired L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysyl-glycinamide.

Preparation of Felypressin: The aforesaid residue, containing the L-cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysyl-glycinamide, is dissolved in 20,000 parts by volume of 0.01 normal acetic acid and is then oxidized by passing air into the solution at a pH of 6.5 to 8.0 for 1 hour. The solution, which contains Felypressin, is adjusted to a pH of 4.0 to 5.0, whereupon 100 parts by weight of sodium chloride are added and the mixture evaporated to dryness, yielding a dry powder of good stability. It can be stored, and yields a clear solution, e.g., in water or other appropriate solvent. The solution may be used directly or, if desired, after dilution with water or a sodium chloride solution.

References

Merck Index 3885
Kleeman & Engel p. 385
I.N. p. 414
Boissonnas, R. and Guttmann, S.; U.S. Patent 3,232,923; February 1, 1966; assigned to Sandoz AG, Switzerland

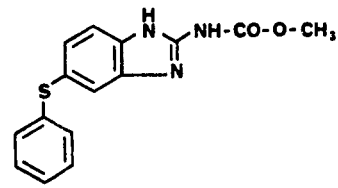
FENBENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: 5-Phenylmercapto-benzimidazole-2-methyl-carbamate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 43210-67-9

Trade Name	Manufacturer	Country	Year Introduced
Panacur	Hoechst	W. Germany	1980

Raw Materials

S-Methyl thiourea
Chloroformic acid methyl ester
3,4-Diamino-diphenyl-thioether

Manufacturing Process

20.9 g of S-methyl-thiourea were dissolved in 27 ml of water with 13.5 ml of chloroformic acid methyl ester. Then, 45.7 ml of 25% sodium hydroxide solution were added dropwise, while stirring, at a temperature of 5°C to 10°C. After having stirred for 20 minutes, the reaction mixture was combined with 27 ml of glacial acetic acid, 100 ml of water and 29 g of 3,4-diamino-diphenyl-thioether. Stirring was continued for 90 minutes at a temperature of 85°C, during which time methyl-mercaptan was separated. After having allowed the whole to cool and stand overnight, the 5-phenylmercapto-benzimidazole-2-methyl-carbamate that had formed was filtered off with suction. After recrystallization from a mixture of glacial acetic acid and methanol, 14 g of 4-phenylmercapto-benzimidazole-2-methyl-carbamate melting at 233°C were obtained.

References

Merck Index 3891
OCDS Vol. 3 p. 176 (1984)
DOT 14 (1) 45 (1978)
I.N. p. 414
Loewe, H., Urbanietz, J., Kirsch, R. and Duwel, D.; U.S. Patent 3,984,561; October 5, 1976; assigned to Hoechst AG
Loewe, H., Urbanietz, J., Kirsch, R. and Duwel, D.; U.S. Patent 3,954,791; May 4, 1976; assigned to Hoechst AG

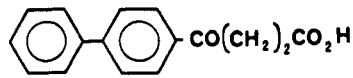
FENBUFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 3-(4-Biphenylylcarbonyl)propionic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 36330-85-5

Trade Name	Manufacturer	Country	Year Introduced
Cinopal	Cyanamid	Italy	1976
Lederfen	Cyanamid	W. Germany	1979
Lederfen	Lederle	U.K.	1979
Cinopal	Opopharma	Switz.	1979
Napanol	Lederle	Japan	1980
Cinopal	Cyanamid	France	1971
Bufemid	Lederle	–	–

Raw Materials

Biphenyl
Succinic anhydride
Aluminum chloride

Manufacturing Process

135 g of aluminum chloride is dissolved in 500 ml of nitrobenzene, the solution being held

below 10°C by external cooling. A finely ground mixture of 50 g of succinic anhydride and 75 g of biphenyl is added to the stirred solution, the temperature being held below 10°C. It is then held at room temperature for four days. After pouring the reaction mixture into a solution of 150 ml of concentrated hydrochloric acid in 1 liter of ice water, the nitrobenzene is removed by steam distillation. The solid is collected, dissolved in 4 liters of 3% hot sodium carbonate solution, clarified, and reprecipitated by the addition of excess 6N sulfuric acid solution. The crude product is collected, dried, and recrystallized from ethanol to give the pure subject compound, MP 185°C to 187°C.

References

Merck Index 3893
DFU 1 (1) 26 (1976)
Kleeman & Engel p. 386
OCDS Vol. 2 p. 126 (1980)
DOT 13 (4) pp. 133, 136 (1977)
I.N. p. 416
Tomcufcik, A.S., Child, R.G. and Sloboda, A.E.; U.S. Patent 3,784,701; January 8, 1974; assigned to American Cyanamid Co.

FENDILINE HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: γ-phenyl-N-(1-phenylethyl)benzenepropanamine hydrochloride

Common Name: N-(1-phenylethyl)-3,3-diphenyl-propylamine

Structural Formula:

$$(C_6H_5)_2CHCH_2CH_2NH\overset{\displaystyle CH_3}{\overset{|}{C}}HC_6H_5 \cdot HCl$$

Chemical Abstracts Registry No.: 13636-18-5; 13042-18-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sensit	Thiemann	W. Germany	1974
Sensit F	Ravasini	Italy	1981
Difmecor	UCM-Difme	Italy	–
Fendilar	Spa	Italy	–

Raw Materials

γ,γ-Diphenylpropylamine	Hydrogen
Acetophenone	Hydrogen chloride

Manufacturing Process

21.13 grams of γ,γ-diphenyl-propylamine and 12.01 grams of acetophenone are hydrogenated in 200 ml of methanol at 55°C and a pressure of 10 atmospheres in the presence of palladium charcoal. On filtration of the catalyst the solution is concentrated and the remainder is distilled in vacuo at a pressure of 0.3 Hg mm. The main distillate is collected at 206° to 210°C. 25.38 grams of N-[1'-phenylethyl-(1')]-1,1-diphenyl-propyl-(3)-amine are obtained.

The product is dissolved in 134 ml of 96% ethanol whereupon 26.8 ml of concentrated hydrochloric acid and 201 ml of water are added while cooling with ice-water. The pre-

cipitate is filtered off and dried in vacuo at 100°C. 22.98 grams of N-[1'-phenylethyl)-(1')]-1,1-diphenyl-propyl-(3)-amine hydrochloride are obtained. MP 200° to 201°C. On recrystallization from 285 ml of a 2:1 mixture of water and 96% ethanol the melting point remains unchanged.

References

Merck Index 3903
Kleeman & Engel p. 389
DOT 10 (12) 337 (1974)
I.N. p. 417
Harsányi, K., Korbonits, D., Takács, K., Tardos, L. and Leszkovszky, G.; U.S. Patent 3,262,977; July 26, 1966; assigned to Chinoin Gyógyszer-és Vegyeszeti Termékek, Hungary

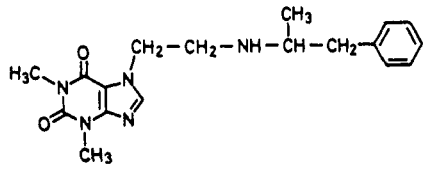
FENETHYLLINE HCl

Therapeutic Function: Central stimulant

Chemical Name: 3,7-Dihydro-1,3-dimethyl-7-[2-[(1-methyl-2-phenylethyl)amino] ethyl]-1H-purine-2,6-dione

Common Name: Theophyllineethylamphetamine

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1892-80-4; 3736-08-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Captagon	Homburg	W. Germany	1961
Gelosedine	Bayer	France	1964
Captagon	Gerda	France	–
Fitton	Teva	Israel	–

Raw Materials

7-(β-Chloroethyl)-theophylline
α-Methyl-β-phenyl ethylamine
Hydrogen chloride

Manufacturing Process

1 mol of 7-(β-chloroethyl)-theophylline and 2½ mols of α-methyl-β-phenyl ethylamine are heated for 6 hours in an oil bath, if necessary with addition of alcohol or toluene. The reaction mixture is diluted with alcohol and acidified with alcoholic hydrochloric acid. The crystalline mass formed is filtered with suction and extracted by boiling with alcohol. A product having a melting point of 237°C to 239°C is formed. With prolonged extraction by boiling with alcohol, the melting point of the mass falls, preferably due to a change in modification, to 227°C to 229°C. However, analysis shows that both products are the pure condensation product.

Instead of the chloroethyl theophylline, it is also possible to use the corresponding bromine derivative. It was found that in this way the process is facilitated and the yield is improved.

References

Merck Index 3906
Kleeman & Engel p. 390
OCDS Vol. 1 p. 425 (1977)
I.N. p. 418
Kohlstaedt, E. and Klingler, K.H.; U.S. Patent 3,029,239; April 10, 1962; assigned to Chemie-werke Homburg

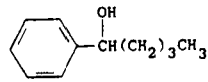
FENIPENTOL

Therapeutic Function: Choleretic

Chemical Name: α-Butylbenzenemethanol

Common Name: Phenylpentanol

Structural Formula:



Chemical Abstracts Registry No.: 583-03-9

Trade Name	Manufacturer	Country	Year Introduced
Pancoral	Eisai	Japan	1973
Euralan	Badrial	France	1974
Billicol	Violoni-Farmavigor	Italy	–
Cholipin	Boehr. Ingel.	Italy	–
Critichol	Angelini	Italy	–
Epatolark	Farm. Mil.	Italy	–
Eprox	Off	Italy	–
Fabil-Valeas	Valeas	Italy	–
Florobil	Scalari	Italy	–
Kol	Mitim	Italy	–
Liverpen	Guidil	Italy	–
Pentabil	Off	Italy	–
Suiclisin	Nikken	Japan	–

Raw Materials

Benzaldehyde
Butyl bromide
Magnesium

Manufacturing Process

The 1-phenyl-pentanol-(1) may be prepared in any convenient manner. Benzaldehyde may be reacted with n-butyl-magnesium bromide, and after purification 1-phenyl-pentanol-(1) is obtained in the form of a colorless oil at room temperature.

References

Merck Index 3909

Kleeman & Engel p. 391
DOT 10 (6) 203 (1974)
I.N. p. 418
Scheffler, H. and Engelhorn, R.; U.S. Patent 3,084,100; April 2, 1963; assigned to Dr. Karl Thomae G.m.b.H.

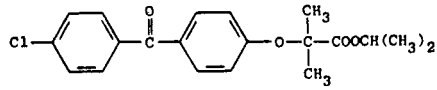
FENOFIBRATE

Therapeutic Function: Antihyperlipoproteinemic

Chemical Name: 2-[4-(4-Chlorobenzoyl)phenoxy] -2-methylpropanoic acid-1-methylethyl ester

Common Name: Procetofen

Structural Formula:



Chemical Abstracts Registry No.: 49562-28-9

Trade Name	Manufacturer	Country	Year Introduced
Lipantyl	Fournier	France	1975
Lipanthyl	Fournier	Switz.	1975
Lipanthyl	Pharma Holz	W. Germany	1978
Lipanthyl	Nativelle	Italy	1979
Lipidax	UCB-Smit	Italy	1979
Ankebin	Volpino	Argentina	—
Elasterin	Phoenix	Argentina	—
Fenobrate	Gerardo Ramon	Argentina	—
Fenolibs	L.I.B.S.	France	—
Lipanthyl	Falorni	Italy	—
Lipidil	Ibirn	Italy	—
Lipoclar	Farmacosmici	Italy	—
Lipofene	Selvi	Italy	—
Liposit	S.I.T.	Italy	—
Nolipax	Biomedica Foscama	Italy	—
Procetoken	Bernabo	Argentina	—
Protolipan	Millet	Argentina	—
Sedufen	Microsules	Argentina	—

Raw Materials

4-Hydroxy-4'-chlorobenzophenone
Sodium hydroxide
Thionyl chloride
Acetone
Chloroform
Isopropanol

Manufacturing Process

(a) Preparation of p-(4-chlorobenzoyl)-phenoxyisobutyric acid: 1 mol of 4-hydroxy-4'-chlorobenzophenone is dissolved in anhydrous acetone and then 5 mols of powdered sodium hydroxide is added. The corresponding sodium phenoxide precipitates. Refluxing is effected, and then, 1.5 mols of $CHCl_3$ diluted with anhydrous acetone is added and the resulting mixture is refluxed for 10 hours. After cooling, water is added, the acetone is evaporated, the

aqueous phase is washed with ether and acidified and the organic phase is redissolved in ether and extracted into a solution of bicarbonate. The bicarbonate solution is then acidified to obtain the desired acid, having a melting point of 185°C, with a yield of 75%.

(b) Preparation of fenofibrate: 1 mol of the acid obtained is converted into its acid chloride using thionyl chloride (2.5 mols). 1 mol of the acid chloride is then condensed with 1.05 mol of isopropyl alcohol in the presence of 0.98 mol of pyridine in an inert solvent such as benzene.

Since traces of SO_2 (which has a bad smell) may be obtained from the thionyl chloride, it is preferable to avoid this disadvantage by carrying out the esterification directly.

References

Merck Index 3912
Kleeman & Engel p. 392
I.N. p. 419
Mieville, A.; U.S. Patent 3,907,792; September 23, 1975

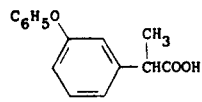
FENOPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: α-methyl-3-phenoxybenzeneacetic acid

Common Name: m-phenoxyhydratropic acid

Structural Formula:



Chemical Abstracts Registry No.: 31879-05-7

Trade Name	Manufacturer	Country	Year Introduced
Fenopron	Dista	U.K.	1974
Feprona	Lilly	W. Germany	1975
Nalfon	Dista	U.S.	1976
Fepron	Lilly	Italy	1978
Nalgesic	Lilly	France	1979
Fenopron	Yamanouchi	Japan	1982
Fenoprex	Lilly	–	–
Progesic	Lilly	–	–

Raw Materials

m-Hydroxyacetophenone
Potassium carbonate
Sodium borohydride
Phosphorus tribromide
Bromobenzene
Copper
Sodium cyanide
Sodium hydroxide

Manufacturing Process

3-Phenoxyacetophenone: A mixture consisting of 908 grams (6.68 mols) of m-hydroxyacetophenone, 4,500 grams (28.6 mols) of bromobenzene, 996 grams (7.2 mols) of anhydrous potassium carbonate, and 300 grams of copper bronze was heated under reflux with

stirring until water evolution was complete, using a Dean-Stark water separator. The mixture was then stirred and refluxed for 24 hours. After cooling to room temperature, the reaction was diluted with an equal volume of $CHCl_3$ and filtered. The filtrate was washed with 5% HCl, then with 5% NaOH, with water, dried over Na_2SO_4 and evaporated in vacuo. The residual oil was distilled through a 15 cm Vigreux column, yielding 918 grams of 3-phenoxy-acetophenone, BP 120° to 121°C (0.09 mm).

α-Methyl-3-Phenoxybenzyl Alcohol: A stirred solution of 700 grams of m-phenoxyacetophenone in 3,000 ml anhydrous methanol was cooled to 0°C in an ice-acetone bath. Sodium borohydride, 136 grams (3.6 mols) was added to this solution in small portions at such a rate that the temperature never rose above 10°C. After borohydride addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 18 hours. It was then stirred and refluxed for 8 hours. About 400 ml of methanol was distilled out and the remaining solution was evaporated to about one-third its original volume in vacuo and poured into ice water. This mixture was extracted twice with ether, acidified with 6 N HCl, and again extracted with ether. The ether extracts were combined, washed with saturated NaCl solution, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residual oil was distilled through a 15 cm Vigreux column, yielding 666 grams of α-methyl-3-phenoxybenzyl alcohol, BP 132° to 134°C (0.35 mm), $n_D^{25} = 1.5809$.

α-Methyl-3-Phenoxybenzyl Bromide: A stirred solution of 1,357 grams of α-methyl-3-phenoxybenzyl alcohol in 5,000 ml anhydrous CCl_4 (predried over molecular sieve) was cooled to 0°C. To this was added 1,760 grams PBr_3, stirring and cooling being maintained at such a rate that the temperature remained at 0° to 5°C, during the addition. The reaction mixture was then allowed to warm to room temperature and was stirred at room temperature overnight (ca 12 hours). The reaction mixture was then poured into ice water and and the organic phase separated. The aqueous phase was extracted with CCl_4 and the combined extracts were washed three times with water, dried over anhydrous sodium sulfate and evaporated to dryness in vacuo to yield 1,702 grams of α-methyl-3-phenoxybenzyl bromide as a heavy viscous oil, $n_D^{25} = 1.5993$.

2-(3-Phenoxyphenyl)Propionitrile: A well-stirred suspension of 316 grams of 98% sodium cyanide in 5,000 ml of anhydrous dimethyl sulfoxide (previously dried over molecular sieve) was warmed to 55° to 60°C and maintained at this temperature while 1,702 grams of α-methyl-3-phenoxybenzyl bromide was slowly added. After the bromide addition was completed, the temperature was raised to 75°C and the mixture stirred at this temperature for 1.5 hours. The mixture was then allowed to cool to room temperature and was stirred overnight at room temperature and then poured into ice water. The resulting aqueous suspension was extracted twice with ethyl acetate, and then with ether. The organic extract was washed twice with a sodium chloride solution, once with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo left an oily residue which was distilled through a 15 cm Vigreux column to yield 1,136 grams of 2-(3-phenoxyphenyl)-propionitrile, BP 141° to 148°C (0.1 mm), $n_D^{25} = 1.5678$.

2-(3-Phenoxyphenyl)Propionic Acid: A mixture of 223 grams of 2-(3-phenoxyphenyl)-propionitrile and 400 grams of sodium hydroxide in 1,600 ml of 50% ethanol was refluxed with stirring for 72 hours. After cooling to room temperature, the reaction mixture was poured into ice water. The resulting solution was washed with ether, acidifed with concentrated HCl, and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo. The residual oil was distilled to yield 203.5 grams (84%) of 2-(3-phenoxyphenyl)propionic acid as a viscous oil; BP 168° to 171°C (0.11 mm), $n_D^{25} = 1.5742$.

References

Merck Index 3913
Kleeman & Engel p. 392
PDR p. 843
OCDS Vol. 2 p. 67 (1980)

DOT 8 (1) 34 (1972) & 9 (9) 373 (1973)
I.N. p. 419
REM p. 1116
Marshall, W.S.; U.S. Patent 3,600,437; August 17, 1971; assigned to Eli Lilly and Company

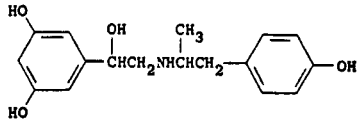
FENOTEROL HYDROBROMIDE

Therapeutic Function: Bronchodilator

Chemical Name: 3,5-dihydroxy-α-[[(p-hydroxy-α-methylphenethyl)amino] methyl] benzyl alcohol hydrobromide

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1944-12-3; 13392-18-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Berotec	Boehr. Ingel.	W. Germany	1972
Berotec	W.B. Pharm	U.K.	1977
Dosberotec	Boehr. Ingel.	Italy	1980
Berotec	Boehr. Ingel.	Switz.	1982
Airum	Promeco	Argentina	–
Berotec	Fher	Spain	–
Partusisten	Boehr. Ingel.	–	–

Raw Materials

3,5-Diacetoxy acetophenone
1-p-Methoxyphenyl-2-benzylamino propane
Hydrogen bromide
Hydrogen chloride
Bromine
Hydrogen

Manufacturing Process

441 grams (1.4 mols) of 3,5-diacetoxy-α-bromo-acetophenone (MP 66°C), prepared by bromination of 3,5-diacetoxy-acetophenone, were added to a solution of 714 grams (2.8 mols) of 1-p-methoxyphenyl-2-benzylamino-propane in 1,000 cc of benzene, and the resulting solution mixture was refluxed for 1 hour. The molar excess of 1-p-methoxy-phenyl-2-benzylamino-propane precipitated out as its hydrobromide. After separation of the precipitated hydrobromide of the amino component, the hydrochloride of 1-p-methoxy-phenyl-2-(β-3',5'-diacetoxyphenyl-β-oxo)-ethyl-benzylamino-propane was precipitated from the reaction solution by addition of an ethanolic solution of hydrochloric acid. The precipitate was separated and, without further purification, was deacetylated by boiling it in a mixture of 2 liters of aqueous 10% hydrochloric acid and 1.5 liters of methanol.

The resulting solution was filtered through animal charcoal and, after addition of 2 liters of methanol, it was debenzylated by hydrogenation at 60°C over palladinized charcoal as a catalyst. After removal of the catalyst by filtration, the filtrate was concentrated by evaporation, whereupon the hydrochloride of 1-p-methoxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-oxo)-ethylamino-propane (MP 244°C) crystallized out. For the purpose of demethylation,

the 350 grams of the hydrochloride thus produced were refluxed for 2 hours with 3.5 liters of aqueous 48% hydrobromic acid. Upon cooling of the reaction solution, 320 grams of 1-p-hydroxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-oxo)-ethylamino-propane hydrobromide (MP 220°C) crystallized out.

220 grams of 1-p-hydroxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-oxo)-ethylamino-propane hydrobromide were dissolved in 1 liter of methanol, the resulting solution was boiled with activated charcoal, the charcoal was filtered off and the filtrate was hydrogenated in the presence of Raney nickel at 60°C and 5 atmospheres gauge. Thereafter, the catalyst was filtered off, the methanolic solution was admixed with a small amount of concentrated hydrobromic acid, and the mixture was evaporated to dryness in vacuo. The residue was stirred with acetone, the mixture was vacuum filtered and the filter cake was recrystallized from a mixture of methanol and ether. The 1-p-hydroxyphenyl-2-(β-3',5'-dihydroxyphenyl-β-hydroxy)-ethylamino-propane hydrobromide thus obtained had a melting point of 222° to 223°C.

References

Merck Index 3914
Kleeman & Engel p. 393
OCDS Vol. 2 p. 38 (1980)
DOT 8 (1) 36 (1972), 9 (1) 21 (1973) & 11 (1) 20 (1975)
I.N. p. 419
Zeile, K., Thoma, O. and Mentrup, A.; U.S. Patent 3,341,593; September 12, 1967; assigned to Boehringer Ingelheim GmbH, Germany

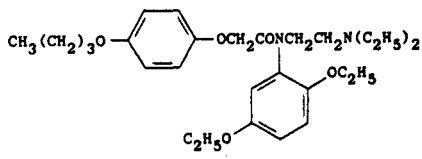
FENOXEDIL

Therapeutic Function: Vasodilator

Chemical Name: 2-(4-butoxyphenoxy)-N-(2,5-diethoxyphenyl)-N-[2-(diethylamino)ethyl]-acetamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 54063-40-0; 27471-60-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Suplexedil	Hepatrol	France	1974

Raw Materials

2,5-Diethoxyaniline
4-Butoxyphenoxy acetyl chloride
2-Diethylamino-1-chloroethane
Triethylamine
Sodium amide

Manufacturing Process

420 grams of 2,5-diethoxy aniline are dissolved in 4 liters of dichloroethane and 230 grams

of triethylamine are added. The mixture is heated, while stirring, with 845 grams of 4-butoxy phenoxy acetyl chloride. The temperature increases towards 40°C. The mixture is then heated for 2 hours at 80°C. After cooling the product is washed with normal hydrochloric acid, then with water, then with normal sodium carbonate and finally with water.

The organic phase is dried over sodium sulfate, filtered, the dichloroethane is evaporated off and the residue is crystallized from ethyl alcohol (95%). The product is dried in the oven and there is thus obtained about 800 grams (yield 90%) of the N-(2,5-diethoxyphenyl)-4-butoxy phenoxy acetamide, MP 101°C.

A vessel provided with a mechanical agitator, a thermometer and a refrigerant, is charged with 49.2 grams of sodamide (90%) in suspension in 300 ml of anhydrous toluene, and a solution of 465 grams of amide obtained as above in 2 liters of anhydrous toluene. The solution is poured in, little by little during 1.5 hours with slight warming. The mixture is maintained for 1 hour at 80°C during which ammonia is evolved. It is cooled to 45°C, there is added, in a single quantity, 170 grams of 2-diethyl-amino-1-chloroethane and the temperature is raised slowly to 100°C and is maintained there for 10 hours.

The mixture is cooled, the organic phase washed with water and dried over sodium sulfate. The toluene is evaporated and the residue taken up in 2 liters of normal acetic acid, with cooling. It is allowed to crystallize in the cold, filtered to remove the insoluble portion and the base precipitated from the filtrate by the addition of sodium carbonate; this is extracted with dichloroethane and the organic phase dried over sodium sulfate. After evaporation of the solvent an oil is distilled, BP 225° to 230°C/0.1 mm, weight 340 grams, yield 58%. The hydrochloride prepared by the action of gaseous hydrogen chloride on this oil in ethyl ether melts at 140°C.

References

Merck Index 3916
Kleeman & Engel p. 395
DOT 11 (2) 58 (1975)
I.N. p. 420
Thuillier, G. and Geffroy, F.; U.S. Patent 3,818,021; June 18, 1974; assigned to CERPHA (Centre Europeen de Recherches Pharmacologiques), France

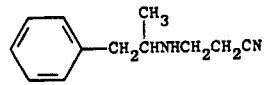
FENPROPOREX

Therapeutic Function: Anorexic

Chemical Name: 3-[(1-Methyl-2-phenylethyl)amino]propanenitrile

Common Name: N-2-Cyanoethylamphetamine

Structural Formula:



Chemical Abstracts Registry No.: 15686-61-0

Trade Name	Manufacturer	Country	Year Introduced
Fenproporex	Chephasaar	W. Germany	1975

Trade Name	Manufacturer	Country	Year Introduced
Fenproporex	Bottu	France	1977
Desobesi	Luer	Brazil	—
Fenorex	Biosintetica	Brazil	—
Lineal	Roussel	—	—
Lipolin	ICN-Usafarma	Brazil	—
Perphoxene	Bottu	France	—
Perphoxene	Siegfried	Switz.	—
Tegisec	Roussel	—	—

Raw Materials

Acrylonitrile
α-Methyl-β-phenylethylamine
Hydrogen chloride

Manufacturing Process

(a) 22 g of acrylonitrile and 27 g of racemic α-methyl-β-phenylethylamine were introduced into a 100 ml round-bottomed flask and left standing for 13 hours at ambient temperature, and then the mixture was boiled under reflux for 12½ hours. The excess acrylonitrile was then evaporated in vacuo and the residue distilled. 27.3 g (yield: 72.6%) of racemic N-(β-cyanoethyl)-α-methyl-β-phenylethylamine were obtained as an oily liquid, BP = 126°C to 127°C/2 mm Hg.

(b) 22 g of the base obtained in (a) were dissolved in 80 ml of anhydrous diethyl ether and an ethereal solution of hydrochloric acid added until the pH value was 1. The salt was filtered off, dried and washed with 10 ml of diethyl ether. 18 g (yield: 68%) of N-(β-cyanoethyl-α-methyl-β-phenylethylamine hydrochloride were obtained, after recrystallization from absolute ethanol, as a white, microcrystalline, odorless powder having a bitter, acid taste; it was fairly soluble in water, ether and benzene. MP = 146°C on a Kofler block.

References

Merck Index 3922
DOT 9 (6) 213 (1973)
I.N. p. 420
Rohrbach, P. and Blum, J.; U.S. Patent 3,485,924; December 23, 1969; assigned to Manufactures J.R. Bottu (France)

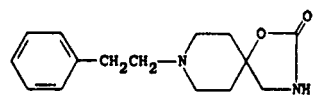
FENSPIRIDE

Therapeutic Function: Bronchodilator

Chemical Name: 8-(2-phenylethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one

Common Name: Decaspiride

Structural Formula:



Chemical Abstracts Registry No.: 5053-06-5; 5053-08-7 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Viarespan	Servier	France	1969
Respiride	Schiapparelli	Italy	1979
Abronquil	Soubeiran Chobet	Argentina	–
Decaspir	Pulitzer	Italy	–
Espiran	Fardeco	Italy	–
Fendel	Sidus	Argentina	–
Fluiden	Lafare	Italy	–
Pneumorel	Biopharma	France	–
Teodelin	Cuatrecasas-Darkey	Spain	–

Raw Materials

1-(2-Phenylethyl)-4-piperidone
Lithium aluminum hydride
Potassium cyanide
Diethyl carbonate

Manufacturing Process

A solution of 192 g of 1-phenethyl-4-hydroxy-4-aminomethyl piperidine in 800 cc of diethyl-carbonate is heated for 2½ hours to reflux at about 80°C in the presence of sodium methylate (prepared for immediate use from 2 g of sodium). After this time, the ethyl alcohol formed during the reaction is slowly distilled while the maximum temperature is reached. The excess ethyl carbonate is distilled under reduced pressure. A crystallized residue is then obtained, which is stirred with 400 cc of water and 400 cc of ether. The solution is filtered and 125 g (77.6%) of practically pure product melting at 232°C to 233°C, are obtained.

The starting material was prepared in a yield of 58% by reduction of the corresponding cyano-hydrin. It in turn was prepared from 1-(2-phenylethyl)-4-piperidone and potassium cyanide to give the cyanohydrin which was reduced by lithium aluminum hydride.

References

Merck Index 3924
Kleeman & Engel p. 397
OCDS Vol. 2 p. 291 (1980)
DOT 5 (4) 130 (1969)
I.N. p. 421
Regnier, G., Canevari, R. and Le Douarec, J.-C.; U.S. Patent 3,399,192; August 27, 1968; assigned to Science Union et Cie, Societe Francaise de Recherche Medicale, France

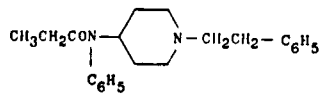
FENTANYL

Therapeutic Function: Narcotic analgesic

Chemical Name: N-phenyl-N-[1-(2-phenylethyl)-4-piperidinylpropanamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 437-38-7

Trade Name	Manufacturer	Country	Year Introduced
Fentanyl	Janssen	W. Germany	1963
Sublimaze	Janssen	U.K.	1965
Fentanest	Carlo Erba	Italy	1965
Sublimaze	McNeil	U.S.	1968
Fentanest	Sankyo	Japan	1972
Fentanyl Le Brun	Le Brun	France	1973
Beatryl	Abic	Israel	—
Haldid	Janssen	—	—
Innovar	McNeil	U.S.	—
Leptanal	Leo	Sweden	—
Thalamonal	Janssen	W. Germany	—

Raw Materials

1-Benzyl-4-piperidone
Lithium aluminum hydride
β-Phenylethyl chloride
Aniline
Propionic anhydride
Hydrogen

Manufacturing Process

To the stirred solution of 5 parts of N-(4-piperidyl)propionanilide, 6.85 parts sodium carbonate, 0.05 part potassium iodide in 120 parts hexone is added portionwise a solution of 3.8 parts β-phenylethyl chloride in 24 parts 4-methyl-2-pentanone. The mixture is stirred and refluxed for 27 hours. The reaction mixture is filtered while hot, and the filtrate is evaporated. The oily residue is dissolved in 160 parts diisopropyl ether and the solution is filtered several times until clear, then concentrated to a volume of about 70 parts. The residue is then cooled for about 2 hours at temperatures near 0°C to yield N-[1-(β-phenylethyl)-4-piperidyl] propionanilide, melting at about 83° to 84°C as described in U.S. Patent 3,141,823.

The starting material is prepared by reacting 1-benzyl-4-piperidone with aniline, reducing the condensation product with lithium aluminum hydride, reacting the product thus obtained with propionic anhydride, then hydrogen.

References

Merck Index 3926
Kleeman & Engel p. 397
PDR pp. 954, 957
OCDS Vol. 1 pp. 299, 306, 309 (1977) & 3 p. 116 (1984)
DOT 1 (1) 1 (1965)
I.N. p. 421
REM p. 1108
Janssen, P.A.J. and Gardocki, J.F.; U.S. Patent 3,141,823; September 4, 1962; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; U.S. Patent 3,164,600; January 5, 1965; assigned to Research Laboratorium Dr. C. Janssen, NV, Belgium

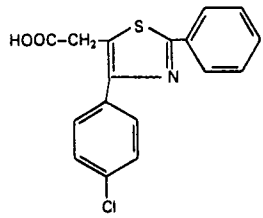
FENTIAZAC

Therapeutic Function: Analgesic, antipyretic and antiinflammatory

Chemical Name: 4-(p-Chlorophenyl)-2-phenyl-thiazol-5-yl-acetic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 18046-21-4

Trade Name	Manufacturer	Country	Year Introduced
Norvedan	LPB	Italy	1975
Norvedan	Nippon Chemiphar	Japan	1982
Donorest	Wyeth	Japan	1982
Domureuma	Medici Domus	Italy	–
Flogene	Polifarma	Italy	–

Raw Materials

Methyl 3-(p-chlorobenzoyl)-3-bromopropionate
Potassium thioacetate
Potassium hydroxide
Benzonitrile
Acetic acid

Manufacturing Process

13.6 g methyl 3-(p-chlorobenzoyl)-3-bromopropionate in 30 ml methanol are added to a solution of 5.6 g potassium thioacetate in 30 ml methanol. Immediate precipitation of KBr is observed. The suspension is refluxed for 10 minutes.

It is cooled to ambient temperature, filtered, and the methanol is evaporated to dryness. 13.2 g methyl 3-(p-chlorobenzoyl)-3-thioacetylpropionate in the form of a chromatographically pure orange-colored oil are obtained.

A suspension of 13.2 g methyl 3-(p-chlorobenzoyl)-3-thioacetylpropionate is agitated in 500 ml of a 2N aqueous solution of KOH for 6 hours at ambient temperature in an atmosphere of nitrogen, followed by extraction with ethyl ether. The aqueous phase, adjusted to a pH equal to 2 with 2N HCl, is extracted with ethyl ether which was washed with water, dried over Na_2SO_4, and finally evaporated to dryness.

9.8 g of crude 3-(p-chlorobenzoyl)-3-mercaptopropionic acid are obtained. By recrystallizing from isopropyl ether there are obtained 8.6 g of pure product, MP 96°C to 97°C (yield: 79%).

1.7 ml benzonitrile and 5.05 ml diethylamine are added to a solution of 4 g 3-(p-chlorobenzoyl)-3-thiol-propionic acid in 50 ml ethanol. The solution is agitated at ambient temperature for 60 minutes in an atmosphere of nitrogen. It is then evaporated to a syrupy consistency and 60 ml 50% aqueous acetic acid are added, whereupon the mixture is refluxed for 60 minutes. It is evaporated to a small volume, adjusted to a pH equal to 8 with a saturated solution of sodium bicarbonate and then extracted with ethyl ether. The aqueous phase is acidified with 2N HCl (Congo red), and then again extracted with ethyl ether. It is dried over Na_2SO_4 and evaporated to dryness. The evaporation residue is recrystallized from benzene and 4 g 4-(p-chlorophenyl)-2-phenyl-thiazol-5-yl-acetic acid are obtained (MP = 152°C to 154°C, yield - 74.3%).

References

Merck Index 3928

DOT 11 (9) 351 (1975) & 15 (7) 325 (1979)
I.N. p. 421
Laboratorio Prodotti Biologici Braglia SpA; British Patent 1,380,507; January 15, 1975
Brown, K.; U.S. Patent 3,476,766; November 4, 1969; assigned to John Wyeth & Brother Ltd.

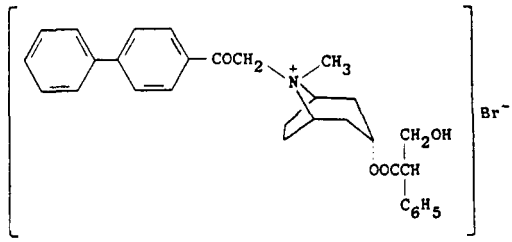
FENTONIUM BROMIDE

Therapeutic Function: Anticholinergic; antispasmodic

Chemical Name: [3(S)-Endo]-8-(2-[1,1'-biphenyl]4-yl-2-oxaethyl)-3-(2-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-azoniabicyclo[3.2.1]octane bromide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 5868-06-4

Trade Name	Manufacturer	Country	Year Introduced
Hoelcesium	Zambon	Italy	1972
Ulcesium	Inpharzam	W. Germany	1978
Dicasten	Fher	Spain	–
Ketoscilium	Zambon	Italy	–

Raw Materials

p-Phenylphenacyl bromide
1-Hyoscyamine

Manufacturing Process

5.50 g (0.02 mol) of p-phenylphenacyl bromide were dissolved in 56 cc of anhydrous acetone previously heated to about 40°C. This solution was added, with stirring, to a solution of 5.70 g (0.02 mol) of 1-hyoscyamine in 43 cc of anhydrous acetone; the reaction solution was maintained at 45°C and stirred for about six hours.

After standing overnight in the refrigerator, the precipitate was collected by filtration and dried in vacuo at 60°C. Yield: 10.2 g; MP = 193°C to 194°C.

References

Merck Index 3930
Kleeman & Engel p. 398
I.N. p. 422
Teotino, U. and Della Bella, D.; U.S. Patent 3,356,682; December 5, 1967 and U.S. Patent 3,436,458; April 1, 1969; both assigned to Whitefin Holding S.A. (Switz.)

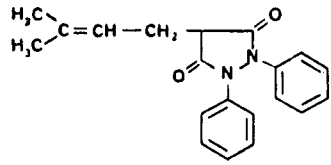
FEPRAZONE

Therapeutic Function: Antiinflammatory

Chemical Name: 1,2-Diphenyl(3,5-dioxo-4-(3'-methyl-2'-butenyl)-pyrazolidine

Common Name: Phenylprenazone, prenazone

Structural Formula:



Chemical Abstracts Registry No.: 30748-29-9

Trade Name	Manufacturer	Country	Year Introduced
Zepelin	De Angeli	Italy	1972
Methrazone	W.B. Pharm.	U.K.	1977
Zepelin	Boehr. Ingel.	W. Germany	1980
Zontal	Fujisawa	Japan	1983
Analud	Unifa	Argentina	–
Brotazona	Escaned	Spain	–
Danfenona	Larma	Spain	–
Grisona	Cusi	Spain	–
Metrazone	Boehr. Ingel.	Spain	–
Naloven	De La Cruz	Spain	–
Nazona	Reig Jofre	Spain	–
Nilatin	Llenas	Spain	–
Prenazon	Inexfa	Spain	–
Rangozona	Mazuelos	Spain	–
Represil	Cecef	Spain	–
Tabrien	Callol	Spain	–
Zepelin	Bender	Austria	–
Zoontal	Boehr. Ingel.	–	–

Raw Materials

Hydrazobenzene
Diethyl-3-methyl-2-butenyl malonate
Sodium
Ethanol

Manufacturing Process

43.8 g (0.237 mol) of hydrazobenzene are added to a solution of sodium ethylate obtained by dissolving 6.55 g (0.285 mol) of sodium in 125 ml of anhydrous ethanol. 59.6 g (0.2612 mol) of diethyl 3-methyl-2-butenyl malonate are then added, with stirring, at the reflux temperature.

The reaction mixture is refluxed for 1 hour, then the solvent is slowly distilled off, the distillation being completed in vacuo. The solid residue so obtained is dissolved in 400 ml of water and washed with ether. The solution is acidified with 10% HCl and the 1,2-diphenyl-3,5-dioxo-4-(3'-methyl-2'-butenyl)-pyrazolidine which separates is purified by crystallization from ethanol (MP 155°C to 156°C).

References

Merck Index 3934
DOT 8 (10) 330 (1972)
I.N. p. 422
Casadio, S. and Pala, G.; U.S. Patent 3,703,528; November 21, 1972; assigned to Instituto de Angeli S.p.A.

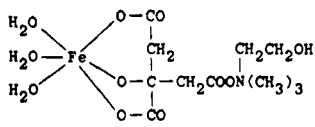
FERROCHOLINATE

Therapeutic Function: Hematinic

Chemical Name: [hydrogen citrato(3—)] triaquoiron, choline salt

Common Name: Iron choline citrate

Structural Formula:



Chemical Abstracts Registry No.: 1336-80-7

Trade Name	Manufacturer	Country	Year Introduced
Ferrolip	Flint	U.S.	1953
Chel-Iron	Kinney	U.S.	1957

Raw Materials

Choline dihydrogen citrate
Tricholine citrate
Ferric hydroxide
Ferric citrate

Manufacturing Process

As described in U.S. Patent 2,575,611, 107 parts of freshly prepared ferric hydroxide are added to 295 parts of choline dihydrogen citrate dissolved in 200 parts of distilled water and heated to approximately 80°C until a homogeneous solution occurs. The resulting reddish brown solution may be used as such or it may be dried by evaporating the water. The dried product is a reddish brown, amorphous solid presenting a glistening surface upon fracture. The dry product is somewhat hygroscopic and is freely soluble in water to give a stable solution. The following paragraph gives an alternative preparation.

One mol of tricholine citrate is dissolved in 6,000 ml of water and two mols of ferric citrate in solid form are added thereto. The reaction mass is then agitated until solution is effected, and until the reaction mass changes from brown to green. Water is removed either under vacuum, or as an azeotrope with benzene or toluene or by heating to a temperature of 110° to 115°C. There is thus obtained a gummy viscous mass which is treated with methanol, about five gallons, whereupon it solidifies, i.e., changes, into a green crystalline compound. Following the treatment with methanol, the mass is filtered and the green compound dried at about 70°C, according to U.S. Patent 2,865,938.

References

Merck Index 3970

I.N. p. 423
Bandelin, F.J.; U.S. Patent 2,575,611; November 20, 1951; assigned to Flint Eaton and Company
Rosenfelder, W.J.; U.S. Patent 2,865,938; December 23, 1958

FERROGLYCINE SULFATE

Therapeutic Function: Hematinic

Chemical Name: Ferroglycine sulfate

Common Name: –

Structural Formula: $(FeSO_4)_x(NH_2CH_2COOH)_y$

Chemical Abstracts Registry No.: 17169-60-7

Trade Name	Manufacturer	Country	Year Introduced
Ferronord	Cooper	U.S.	1956
Fe-Cap	MCP Pure Drugs	U.K.	1970
Bonafer	Remeda	Finland	–
Ferrochel	C.F.C.	Australia	–
Ferrocontin	Napp	U.K.	–
Ferrosanol	Sanol	W. Germany	–
Glycifer	Pharmacia	Sweden	–
Orferon	Pliva	Yugoslavia	–
Plesmet	Napp	U.K.	–

Raw Materials

Ferrous sulfate
Glycine

Manufacturing Process

10.0 g of ferrous sulfate and 2.7 g of glycine are thoroughly mixed and carefully heated under nitrogen to 70°C. Reaction occurs rapidly, and the complex compound is obtained as soon as the color turns uniformly light-brown. After cooling to 20°C, 12.7 g of ferrous sulfate-glycine complex are obtained, which contains 100 mg Fe^{++}-ions per 0.63 g.

References

Merck Index 3972
I.N. p. 12
Rummel, W.; U.S. Patent 2,877,253; March 10, 1959; assigned to Dr. Schwarz Arzneimittelfabrik GmbH, Germany
Rummel, W.; U.S. Patent 2,957,806; October 25, 1960; assigned to Dr. Schwarz Arzneimittelfabrik GmbH, Germany

FERROUS FUMARATE

Therapeutic Function: Hematinic

Chemical Name: Ferrous fumarate

Common Name: –

Structural Formula: $FeC_4H_2O_4$ (exact structure unknown)

Chemical Abstracts Registry No.: 141-01-5

Trade Name	Manufacturer	Country	Year Introduced
Toleron	Mallinckrodt	U.S.	1957
Ircon	Key	U.S.	1960
Tolferain	Ascher	U.S.	1961
Feostat	Westerfield	U.S.	1962
Ferlon	Madland	U.S.	1964
Eldec	Parke-Davis	U.S.	–
Ercofer	Erco	Denmark	–
Fem-Iron	Williams	U.S.	–
Feosol	Menley & James	U.S.	–
Feostim	Westerfield	U.S.	–
Fero-Folic	Abbott	U.S.	–
Fero-Grad	Abbott	U.S.	–
Feroton	Paul Maney	Canada	–
Ferro-Delalande	Delalande	France	–
Ferrofume	Nordic	Canada	–
Ferrolina	Chemie Linz	Austria	–
Ferronat	Galena	Czechoslovakia	–
Ferrone	Wolfs	Belgium	–
Ferrum Hausmann	Hausmann	Switz.	–
Fersaday	Glaxo	–	–
Fersamal	Glaxo	–	–
Ferumat	Continental Pharma	Belgium	–
Firon	Beard Glynn	U.S.	–
Fumafer	Erco	Denmark	–
Fumafer	Aktiva	Sweden	–
Fumasorb	Marion	U.S.	–
Fumiron	Knoll	W. Germany	–
Hematon	Nova	Canada	–
Heptuna	Roerig	U.S.	–
Iberet	Abbott	U.S.	–
Ircon	Lakeside	U.S.	–
Irospan	Fielding	U.S.	–
Mevanin	Beutlich	U.S.	–
Neo-Fer	Nyegaard	Norway	–
Novofumar	Novopharm	Canada	–
Palafer	Beecham	–	–
Pramet	Ross	U.S.	–
Soparon	Sopar	Belgium	–
Tolifer	Elliott-Marion	Canada	–

Raw Materials

Fumaric acid
Sodium carbonate
Ferrous sulfate

Manufacturing Process

Sodium carbonate (53.5 pounds of $Na_2CO_3 \cdot H_2O$) was dissolved in water (40 to 45 gallons)

and fumaric acid (50 pounds) was added slowly. During the addition the solution was stirred and heated. The resulting solution of sodium fumarate, having a pH of 6.8, was added slowly with mixing to a solution of ferrous sulfate (118 pounds $FeSO_4 \cdot 7H_2O$ in 33 gallons of water) having a pH of 3.3, both solutions being maintained at or near boiling temperature during the mixing. The resulting slurry of reddish-brown anhydrous ferrous fumarate was filtered and washed in a centrifuge and dried in a tray drier (15 hours at 110°C). Yield: 63 pounds, 86% of theory. Calculated for $FeC_4H_2O_4$: Fe, 32.9%. Found: Fe, 32.6%. Only 0.2% of ferric iron (Fe^{+++}) was found.

References

Merck Index 3981
PDR pp. 524, 673, 876, 993, 1131, 1344, 1526, 1559, 1569
I.N. p. 447
REM p. 840
Bertsch, H.C. and Lemp, J.F.; U.S. Patent 2,848,366; August 19, 1958; assigned to Mallinckrodt Chemical Works

FIBRINOLYSIN

Therapeutic Function: Thrombolytic enzyme

Chemical Name: Complex protein, molecular weight about 75,000

Common Name: –

Structural Formula: See chemical name

Chemical Abstracts Registry No.: 9001-90-5

Trade Name	Manufacturer	Country	Year Introduced
Actase	Ortho	U.S.	1959
Thrombolysin	MSD	U.S.	1960
Elase	Parke Davis	U.S.	1960
Lyovac	MSD	U.S.	–
Thromboclase	Choay	France	–

Raw Materials

Human blood plasma
Calcium chloride
Oxalic acid
Ammonium sulfate

Manufacturing Process

A 5 gallon drum of frozen plasma oxalated with a known anticoagulant quantity and proportion of oxalic acid and sodium oxalate as described in U.S. Patent 2,394,566 is permitted to stand at room temperature (24° to 26°C) for 24 hours after which the remaining unmelted portion is broken up with an ice pick and a stainless steel warming coil containing running warm water at about 40°C is inserted into the mixture and the mixture stirred. The remaining frozen material is rapidly melted. The warming is then continued with vigorous agitation.

When the temperature of the plasma reaches about 5° to 8°C, the calculated quantity of calcium chloride solution is added in amount which is from 0.2 to 0.3% in excess of that needed to react with and precipitate the anticoagulant. The temperature of the plasma is allowed to rise to about 24°C. At 18° to 24°C strands of fibrin begin to appear and the

vigor of stirring is increased to prevent a gel of fibrin from forming. Stirring is continued for 30 minutes after the fibrin is whipped out to allow for complete conversion of all prothrombin to thrombin and for the antithrombin to completely destroy all thrombin. At the end of this time the stirring is stopped, the fibrin allowed to rise to the surface and the clear serum siphoned off.

If, through failure to stir with enough vigor, a gel forms instead of strands of fibrin, when the temperature reaches about 18°C, the serum can also be obtained from the fibrin by working and kneading the gel in a cheesecloth bag while draining off the clear serum. However, this method is time-consuming and it is preferred to prevent gel formation by very vigorous stirring of the mixture.

The clear serum of this example is an amber liquid free from prothrombin, thrombin, fibrinogen and fibrin. It contains profibrinolysin and is excellently suited to further purification by salt precipitation fractionation, as given below.

The special serum is brought to a temperature of about 4° to 6°C (preferably 5°C) and saturated ammonium sulfate solution added drop by drop with constant stirring to about 24 to 26% of saturation (preferably 25%). The precipitated protein impurities are then centrifuged off and the supernatant brought to about -1° to +1°C (preferably 0°C). The degree of its saturation is then brought to about 28 to 31% of saturation (preferably 29%) by further addition of ammonium sulfate solution with stirring. This further degree of saturation precipitates the profibrinolysin which is collected by centrifugation and separated from soluble impurities. By washing the profibrinolysin several times with ammonium sulfate solution of a strength which is 29% of saturation a practically white solid is obtained which can be freeze-dried (frozen and dried under reduced pressure) to give a dry, white, product containing purified profibrinolysin free from thromboplastin, prothrombin, thrombin, fibrinogen and fibrin, (from U.S. Patent 2,624,691), which is then activated to fibrinolysin.

References

Merck Index 4001
Kleeman & Engel p. 400
PDR p. 1343
I.N. p. 424
REM p. 1038
Loomis, E.C.; U.S. Patent 2,624,691; January 6, 1953; assigned to Parke, Davis & Co.
Singher, H.O.; U.S. Patent 3,136,703; June 9, 1964; assigned to Ortho Pharmaceutical Corp.
Hink, J.H. Jr. and McDonald, J.K.; U.S. Patent 3,234,106; February 8, 1966; assigned to Cutter Laboratories, Inc.

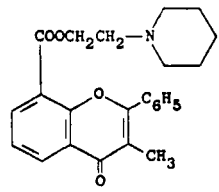
FLAVOXATE HYDROCHLORIDE

Therapeutic Function: Antispasmodic

Chemical Name: 3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxylic acid 2-piperidinoethyl ester hydrochloride

Common Name: 2-piperidinoethyl 3-methylflavone-8-carboxylate

Structural Formula:



(base)

Chemical Abstracts Registry No.: 3717-88-2; 15301-69-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Urispas	SKF	U.S.	1971
Urispas	Syntex	U.K.	1971
Genurin	Recordati	Italy	1973
Spasuret	Asche	W. Germany	1978
Bladderon	Nippon Shinyaku	Japan	1979
Urispas	Negma	France	1981
Spasmal	Ikapharm	Israel	—
Urispadol	Pharmacia	Sweden	—
Urispan	Byk Gulden	—	—
Urispas	Protea	Australia	—

Raw Materials

Salicylic acid
Aluminum chloride
Thionyl chloride
Propionyl chloride
Benzoic anhydride
Piperidinoethanol

Manufacturing Process

A mixture of 13.3 grams of anhydrous aluminum chloride and 100 ml of carbon disulfide is added to 19.4 grams of 2-propionyloxybenzoic acid (prepared from the reaction of propionyl chloride and 2-hydroxybenzoic acid). After an initial evolution of hydrogen chloride, the solvent is removed by distillation and the mixture is heated at 150° to 160°C for 4 hours. The cooled reaction mixture is treated with ice and hydrochloric acid and the product, 2-hydroxy-3-carboxypropiophenone, is obtained from the oily residue by distillation in vacuo.

A mixture of 1.9 grams of 2-hydroxy-3-carboxypropiophenone, 5.0 grams of sodium benzoate and 20.0 grams of benzoic anhydride is heated at 180° to 190°C for 6 hours. A solution of 15.0 grams of potassium hydroxide in 50 ml of ethanol and 20 ml of water is added and refluxed for 1 hour. The mixture is evaporated and the residue after addition of water yields 3-methylflavone-8-carboxylic acid.

To a suspension of 12.0 grams of 3-methylflavone-8-carboxylic acid in 200 ml of anhydrous benzene is added 10.0 grams of thionyl chloride. The mixture is refluxed for 2 hours during which the suspended solid goes into solution. The solvent is completely removed by distillation, the residue extracted with benzene and the extract evaporated to dryness. The product, 3-methylflavone-8-carboxylic acid chloride, is recrystallized from ligroin to give crystals melting at 155° to 156°C.

To 11.0 grams of 3-methylflavone-8-carboxylic acid chloride dissolved in 150 ml of anhydrous benzene is added at room temperature 4.8 grams of piperidinoethanol and the mixture refluxed for 2 to 3 hours. The separated solid is filtered, washed with benzene and dried. The product, piperidinoethyl 3-methylflavone-8-carboxylate hydrochloride is obtained as a colorless crystalline solid, MP 232° to 234°C, (from U.S. Patent 2,921,070).

References

Merck Index 4018
Kleeman & Engel p. 400
PDR p. 1731
OCDS Vol. 2 p. 392 (1980)
DOT 7 (5) 171 (1971)
I.N. p. 426
REM p. 920
Da Re, P.; U.S. Patent 2,921,070; January 12, 1960; assigned to Recordati-Laboratorio Farmacologico SpA, Italy

Da Re, P.; U.S. Patent 3,350,411; October 31, 1967; assigned to Societe d'Exploitation Chimiques et Pharmaceutiques Seceph SA, Switzerland

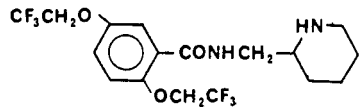
FLECAINIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: N-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 54143-55-4

Trade Name	Manufacturer	Country	Year Introduced
Tambocor	Kettelhack	W. Germany	1982
Tambocor	Riker	U.K.	1983

Raw Materials

2-Aminomethylpiperidine
2,2,2-Trifluoroethyl-2,5-bis(2,2,2-trifluoroethoxy)benzoate
Hydrogen chloride

Manufacturing Process

Under a nitrogen atmosphere 2-aminomethylpiperidine (0.249 mol, 28.4 g) is treated dropwise over 25 minutes with 2,2,2-trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (0.0249 mol, 10.0 g). After 3 hours 50 ml of benzene is added to the thick mixture and stirred for about 40 hours at 45°C. The mixture is then concentrated under vacuum with heating to remove the volatile components. The residue solidifies after cooling, is steam distilled for further purification and is separated by filtration and extracted into dichloromethane. The dichloromethane solution is washed with saturated sodium chloride solution, and the organic layer is dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration and 4 ml of 8.4 N hydrogen chloride in isopropanol is added to the dichloromethane solution with stirring.

After 2 hours the mixture is cooled to about 0°C and the crude product is collected by filtration, washed with diethyl ether and dried in a vacuum oven. After treatment with decolorizing charcoal and recrystallization from an equivolume mixture of isopropanol and methanol, the product, 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide hydrochloride has a MP of 228°C to 229°C.

References

Merck Index 4019
DFU 2 (9) 586 (1977)
OCDS Vol. 3 p. 59 (1984)
DOT 18 (10) 549 (1974), 19 (2) 112 & (5) 252 (1983)
I.N. p. 426
Banitt, E.H. and Brown, W.R.; U.S. Patent 3,900,481; August 19, 1975; assigned to Riker Laboratories, Inc.

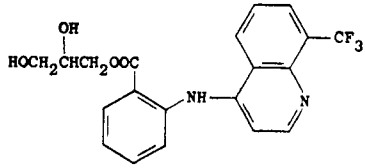
FLOCTAFENINE

Therapeutic Function: Analgesic

Chemical Name: 2-[[8-(trifluoromethyl)-4-quinolinyl] amino] benzoic acid 2,3-dihydroxypropyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 23779-99-9

Trade Name	Manufacturer	Country	Year Introduced
Idarac	Diamant	France	1976
Idarac	Roussel Maestretti	Italy	1977
Idarac	Albert Roussel	W. Germany	1978
Floktin	Yurtoglu	Turkey	–
Idalon	Roussel	–	–

Raw Materials

o-Trifluoromethylaniline
Ethoxymethylene ethyl malonate
Phosphorus oxychloride
Methyl anthranilate
2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane
Sodium hydride
Hydrogen chloride

Manufacturing Process

Step A: Ortho-Trifluoromethylanilinomethylene Ethyl Malonate – A mixture of 54.8 grams of ortho-trifluoromethylaniline and 73.5 grams of ethoxymethylene ethyl malonate was heated to 120°C under an inert atmosphere and maintained for 1 hour at this temperature while distilling off the ethanol formed. The mixture was cooled and the elimination of ethanol was completed by distillation under reduced pressure. The mixture was cooled to obtain 115 grams of ortho-trifluoromethylanilinomethylene ethyl malonate which was used as is for the following stage. A sample of the product was crystallized from petroleum ether (BP = 65° to 75°C) to obtain a melting point of 94°C.

Step B: 3-Carbethoxy-4-Hydroxy-8-Trifluoromethylquinoline – A mixture of 113 grams of crude ortho-trifluoromethylanilinomethylene ethyl malonate from Step A, and 115 cc of phenyl oxide was heated rapidly under an inert atmosphere. At about 195°C, the ethanol formed began to distill off. At the end of about 30 minutes, the interior temperature reached 250°C and the reaction mixture was heated to reflux. Reflux was maintained for 1 hour and the mixture was then cooled, 25 cc of acetone were added and the mixture was allowed to crystallize. The mixture was filtered and the crystals thus formed were washed and dried to obtain 71.5 grams of 3-carbethoxy-4-hydroxy-8-trifluoromethylquinoline with a melting point of 210° to 214°C, which was used as is for the following stage. A sample of this product was crystallized from ethanol to show a melting point of 216°C.

Step C: 3-Carboxy-4-Hydroxy-8-Trifluoromethylquinoline – 70 grams of crude 3-carbethoxy-4-hydroxy-8-trifluoromethylquinoline, obtained in Step B, were introduced under an inert atmosphere into a mixture of 300 cc of water and 100 cc of aqueous 10 N solution of sodium hydroxide. The reaction mixture was heated to reflux and maintained there for 2 hours and forty-five minutes. The solution obtained was poured over a mixture of water, ice and 100 cc of aqueous 11.8 N solution of hydrochloric acid. The precipitate thus formed was isolated by filtration, washed with water and introduced into a solution of 20 grams of sodium bicarbonate in 2 liters of water.

The mixture was heated to 90°C and filtered to remove slight persisting insolubles. The filtrate was acidified with acetic acid to bring the pH to about 5.5 and the precipitate formed was isolated by filtration, washed and dried to obtain 58 grams of 3-carboxy-4-hydroxy-8-trifluoromethylquinoline having a melting point of 290° to 292°C, which was used as is for the following stage. A sample of the product was crystallized from hot and cold acetone, treated with charcoal to obtain pure 3-carboxy-4-hydroxy-8-trifluoromethylquinoline having a melting point of 292°C.

Step D: 4-Hydroxy-8-Trifluoromethylquinoline – Under an inert atmosphere, 56.5 grams of crude 3-carboxy-4-hydroxy-8-trifluoromethylquinoline, obtained in Step C were introduced into 110 cc of phenyl oxide. The reaction mixture was rapidly heated to reflux and maintained at reflux for an hour and fifteen minutes. The reaction mixture was cooled to about 50°C and 20 cc of isopropyl ether were added thereto. The mixture was cooled to 20°C and allowed to crystallize. The precipitate formed was isolated by filtration, washed and dried to obtain 45.8 grams of 4-hydroxy-8-trifluoromethylquinoline having a melting point of 180°C. A sample of this product was crystallized from acetone, treated with charcoal to obtain pure 4-hydroxy-8-trifluoromethylquinoline having a melting point of 180°C.

Step E: 4-Chloro-8-Trifluoromethylquinoline – 44.3 grams of crude 4-hydroxy-8-trifluoromethylquinoline obtained in Step D were introduced in small amounts into 130 cc of phosphorus oxychloride and then the reaction mixture was held for 15 minutes at ambient temperature and heated to reflux and maintained at reflux for 1 hour. The mixture was cooled and excess phosphorus oxychloride was removed by distillation under reduced pressure. Water, ice, and then 80 cc of aqueous solution of ammonia at 22°Bé were added to the residue and the mixture was stirred and the aqueous phase was extracted with ether. The ethereal extracts were washed with a dilute aqueous solution of ammonia, then with water, dried, treated with charcoal and concentrated to dryness to obtain 45.4 grams of 4-chloro-8-trifluoromethylquinoline having a melting point of 78°C, which was used as is for the preparation of 4-(ortho-methoxycarbonylphenylamino)-8-trifluoromethylquinoline. A sample of crude 4-chloro-8-trifluoromethylquinoline was crystallized from petroleum ether (BP = 65° to 75°C) to get a product with a melting point of 78°C.

Step F: 4-(Ortho-Methoxycarbonyl)-Phenylamino-8-Trifluoromethylquinoline – Into 100 cc of aqueous 2 N solution of hydrochloric acid, 23.15 grams of crude 4-chloro-8-trifluoromethylquinoline, obtained in Step E, then 15.85 grams of methyl anthranilate were introduced. The reaction mixture was heated to reflux and maintained there for 50 minutes. The mixture was cooled and the crystallation developed. The precipitate formed was recovered by filtration and introduced into 300 cc of a saturated aqueous solution of sodium bicarbonate. The mixture was agitated, methylene chloride was added and the mixture agitated and filtered to remove persisting insolubles. The organic phase was separated by decantation, washed with water and concentrated to dryness. The residue was crystallized from methanol to obtain 21.3 grams of 4-(ortho-methoxy-carbonylphenylamino)-8-trifluoromethylquinoline with a melting point of 176°C.

Step G: 4-[Ortho-(2',3'-Dihydroxypropyloxycarbonyl)-Phenyl]-Amino-8-Trifluoromethylquinoline Acetonide – 100 cc of toluene were added to 80 cc of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane and the toluene was distilled off under reduced pressure to eliminate the water present. To the anhydrous 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane thus obtained, 0.25 gram of an oily 50% suspension of sodium hydride and then 21.3 grams of 4-

(ortho-methoxycarbonylphenylamino)-8-trifluoromethylquinoline were added under inert atmosphere. The mixture was agitated for 5 hours at 85°C under a vacuum of 50 to 100 mm of mercury. After cooling, an aqueous solution of sodium chloride was added to the reaction mixture and it was stirred. The aqueous phase was extracted with methylene chloride and the methylene chloride extracts were washed with water, dried and concentrated to dryness by distillation under reduced pressure.

The residue was washed with petroleum ether (BP 65° to 75°C), dried and crystallized from isopropyl ether to obtain 23.8 grams of 4-[ortho-(2',3'-dihydroxypropyloxycarbonyl)-phenyl]-amino-8-trifluoromethylquinoline acetonide having a melting point of 108°C.

Step H: Preparation of 4-[Ortho-(2',3'-Dihydroxypropyloxycarbonyl)-Phenyl]-Amino-8-Trifluoromethylquinoline – Into a mixture of 60 cc of water and 12 cc of aqueous solution of 22°Bé hydrochloric acid there was introduced 19.8 grams of 4-[ortho-(2',3'-dihydroxypropyloxycarbonyl)-phenyl]-amino-8-trifluoromethylquinoline acetonide (obtained in Step G) and the temperature of the reaction mixture was raised to 95°C and maintained at this temperature for 15 minutes. The mixture was cooled to 0°C and crystallization was allowed. The crude hydrochloride was recovered by filtration, washed and introduced into a mixture of 60 cc of dimethylformamide, 40 cc of water and 10 cc of triethylamine.

Dissolution and the crystallization occurred and the precipitate was recovered by filtration and was washed and dried to obtain 16 grams of crude base having a melting point of 179° to 180°C. The crude base was crystallized from methanol with treatment with charcoal to obtain 11.95 grams of 4-[ortho-(2',3'-dihydroxypropyloxycarbonyl)-phenyl]-amino-8-trifluoromethylquinoline with a melting point of 179° to 180°C. The product is soluble in ether, chloroform and methylene chloride and insoluble in water.

References

Merck Index 4021
DFU 1 (2) 59 (1976)
Kleeman & Engel p. 401
OCDS Vol. 3 p. 184 (1984)
DOT 13 (4) 143 (1977)
I.N. p. 427
Allais, A. and Meier, J.; U.S. Patent 3,644,368; February 22, 1972; assigned to Roussel-UCLAF, France

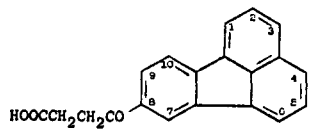
FLORANTYRONE

Therapeutic Function: Hydrocholeretic

Chemical Name: γ-Oxo-8-fluoranthenebutanoic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 519-95-9

Trade Name	Manufacturer	Country	Year Introduced
Zanchol	Searle	U.S.	1957
Bilyn	Janus	Italy	–
Cistoplex	Borromeo	Italy	–
Idroepar	Beolet	Italy	–
Zanchol	Dainippon	Japan	–

Raw Materials

Fluoranthene
Succinic anhydride

Manufacturing Process

50 g of fluoranthene and 26 g of succinic anhydride in 500 cc of nitrobenzene were treated at 0°C to 5°C with 75 g of anhydrous aluminum chloride. The temperature was held at 0°C for 4 hours and then allowed gradually to come to room temperature. The reaction mixture was allowed to stand for 16 hours. The reaction mixture was then worked up. In so doing, the reaction mixture was decomposed with dilute HCl, the nitrobenzene was removed by steam distillation and the residue after filtration was dissolved in hot sodium carbonate solution and filtered free of a small amount of nonacidic material. Precipitation from solution with HCl gave a light yellow product which crystallized from a 50-50 mixture of dioxane-alcohol as fine platelets which melted at 192°C to 194°C and showed a neutral equivalent of 308 which corresponds closely to the theoretical value of 302 for β-fluoranthoylpropionic acid.

25 g of the crude acid was dissolved in 100 cc of water containing 13 g of sodium carbonate. On cooling a thick syrup was obtained. On dilution to 1 liter precipitation started and after standing 16 hours, the solid which separated was filtered (filtrate treated as below), suspended in water, acidified with HCl and filtered. Crystallization from alcohol gave a light yellow material melting at 199°C to 200°C and having a neutral equivalent of 303.

The filtrate mentioned above, upon acidification thereof with HCl gave a darker acid which melted over a wide range, but had a neutral equivalent which also corresponds to that of β-fluoranthoylpropionic acid.

References

Merck Index 4023
Kleeman & Engel p. 403
I.N. p. 427
Fancher, O.E.; U.S. Patent 2,560,425; July 10, 1951; assigned to Miles Laboratories, Inc.

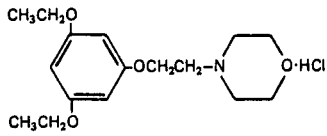
FLOREDIL HYDROCHLORIDE

Therapeutic Function: Coronary stabilizer

Chemical Name: 1-(3′,5′-Diethoxyphenoxy)-2-morpholinoethane hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53731-36-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Carfonal	Lafon	France	1973

Raw Materials

Sodium
Ethanol
3,5-Diethoxyphenol
1-Chloro-2-morpholinoethane hydrochloride

Manufacturing Process

Starting from 2.3 g (0.1 g atom) of sodium in 60 cc ethanol, 9.1 g (0.05 mol) of 3,5-diethoxyphenol in 25 cc of ethanol, and 9.3 g (0.05 mol) of 1-chloro-2-morpholinoethane hydrochloride in 15 cc of ethanol, 12 g (yield 72.4%) of white crystals melting at 183°C to 184°C were obtained after recrystallization from 50 cc of boiling isopropanol, which were soluble in water, slightly soluble in ethanol, and insoluble in hydrocarbons.

References

Merck Index 4024
Kleeman & Engel p. 403
DOT 9 (7) 285 (1973)
I.N. p. 428
Lafon, L.; British Patent 1,262,785; February 9, 1972; assigned to Orsymonde

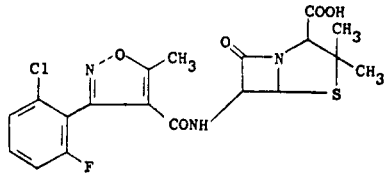
FLOXACILLIN

Therapeutic Function: Antibacterial

Chemical Name: 6-[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: Flucloxacillin; 3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 5250-39-5

Trade Name	Manufacturer	Country	Year Introduced
Floxapen	Beecham	U.K.	1970
Clupen	Fujisawa	Japan	1970
Staphylex	Beecham	W. Germany	1972
Flupen	Alfa	Italy	1974
Flopen	C.S.L.	Australia	–
Fluclox	Ayerst	–	–

Trade Name	Manufacturer	Country	Year Introduced
Heracillin	Astra	–	–
Penplus	Farma Labor	Italy	–

Raw Materials

2-Chloro-6-fluorobenzaldoxime
Methyl acetoacetate
6-Amino-penicillanic acid
Sodium hydroxide
Chlorine
Sodium methoxide
Thionyl chloride

Manufacturing Process

3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylic acid, MP 206° to 207°C, was obtained by chlorinating 2-chloro-6-fluorobenzaldoxime, then condensing the resulting hydroxamoyl chloride with methyl acetoacetate in methanolic sodium methoxide and hydrolyzing the resulting ester with hot alkali. The acid chloride resulted from treatment of the acid with thionyl chloride.

A suspension of 6-aminopenicillanic acid (36.4 grams) in water was adjusted to pH 7.2 by the addition of N aqueous sodium hydroxide and the resulting solution was treated with a solution of 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride (46.1 grams) in isobutyl methyl ketone. The mixture was stirred vigorously for 1½ hours and then filtered through Dicalite. The layers were separated and the isobutyl methyl ketone layer was shaken with saturated brine. Then, precipitation of the sodium salt only took place after dilution of the mixture with ether. In this way there was obtained 60.7 grams of the penicillin sodium salt having a purity of 88% as determined by alkalimetric assay.

References

Merck Index 4025
Kleeman & Engel p. 405
OCDS Vol. 1 p. 413 (1977)
DOT 7 (1) 18 (1971)
I.N. p. 429
REM p. 1201
Nayler, J.H.C.; U.S. Patent 3,239,507; March 8, 1966; assigned to Beecham Group Limited, England

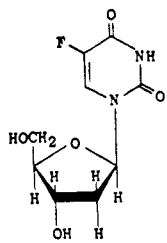
FLOXURIDINE

Therapeutic Function: Antiviral; cancer chemotherapy

Chemical Name: 2'-deoxy-5-fluorouridine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 50-91-9

Trade Name	Manufacturer	Country	Year Introduced
FUDR	Roche	U.S.	1971

Raw Materials

Bacterium *Streptococcus fecalis*
Nutrient medium
5-Fluorouracil
Thymidine

Manufacturing Process

Cells of *Streptococcus fecalis* (ATCC-8043) were grown in the AOAC folic acid assay medium [Lepper, *Official and Tentative Methods of the Association of Official Agricultural Chemists,* Washington, D.C., 7th edition, 784 (1950)], supplemented with 2 mg per liter of thymine; following the teachings of Prusoff, *Proc. Soc. Exp. Biol. & Med.* 85, 564 (1954). After 20 hours of incubation at 37°C, the cells were harvested by centrifugation. The collected cells were washed three times with four volumes of potassium phosphate buffer solution (M/15 aqueous KH_2PO_4 solution, adjusted to pH 8.0 by addition of 2 N aqueous KOH) and the wet cells were weighed. The cells were finally suspended in the above potassium phosphate buffer solution and ground in a glass tissue homogenizer.

An amount of enzyme preparation equivalent to 900 mg of wet cells was made up to 25 ml with the above potassium phosphate buffer solution. 150 mg (1.15 mmol) of 5-fluorouracil and 1.0 gram of thymidine (4.12 mmol) were dissolved in 15 ml of the above potassium phosphate buffer solution. The mixture was incubated at 37°C for 18 hours. After this time, enzyme action was stopped by the addition of four volumes of acetone and one volume of peroxide-free diethyl ether. The precipitated solids were removed by filtration, and the filtrate was evaporated under nitrogen at reduced pressure until substantially all volatile organic solvent had been removed. About 20 ml of aqueous solution, essentially free of organic solvent, remained. This solution was diluted to 100 ml with distilled water.

Ten microliters of this solution were submitted to descending chromatography on a paper buffered with 0.2 N KH_2PO_4 (pH 7.8), using a solvent mixture of tertiary amyl alcohol:-water:n-butyl ether (80:13:7 by volume). A spot visible under ultraviolet light and having R_f = 0.55 was leached with 0.1 N HCl and assayed for deoxyribose by the method of Stumpf, *J. Biol. Chem.* 169, 367 (1947). This analysis indicated the presence of a minimum of 85.5 mg (0.35 mmol) of 2'-deoxy-5-fluorouridine in the protein-free reaction mixture according to U.S. Patent 2,885,396. An alternate route from 5-fluorouracil via the mercury derivative, through toluoyl deoxyuridines and then toluoyl removal to give floxuridine is described in U.S. Patent 3,041,335.

References

Merck Index 4026
PDR p. 1485
DOT 8 (2) 63 (1972)
I.N. p. 428
REM p. 1155
Heidelberg, C. and Duschinsky, R.; U.S. Patent 2,885,396; May 5, 1959
Hoffer, M.; U.S. Patent 2,949,451; August 16, 1960; assigned to Hoffmann-La Roche Inc.
Duschinsky, R., Farkas, W.G. and Heidelberger, C.; U.S. Patent 2,970,139; January 31, 1961
Hoffer, M.; U.S. Patent 3,041,335; June 26, 1962; assigned to Hoffmann-La Roche Inc.

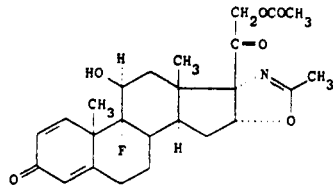
FLUAZACORT

Therapeutic Function: Antiinflammatory

Chemical Name: 21-(Acetyloxy)-9-fluoro-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno-[17,16-d] oxazole-3,20-dione

Common Name: Fluazacortenol acetate

Structural Formula:



Chemical Abstracts Registry No.: 19888-56-3

Trade Name	Manufacturer	Country	Year Introduced
Azacortid	Richter	Italy	1975
Azacortid	Lepetit	France	1981

Raw Materials

Pregna-1,4,9(11)-triene-21-ol-3,20-dione-[17α,16α-d] -2'-methyloxazoline-21-acetate
N-Bromoacetamide
Sodium hydroxide
Hydrogen fluoride

Manufacturing Process

To a solution of 2.4 g of pregna-1,4,9(11)-triene-21-ol-3,20-dione-[17α,16α-d] -2'-methyloxazoline 21-acetate in 24 ml of tetrahydrofuran, 12.8 ml of 0.46 N perchloric acid are added at 15°C under stirring. N-bromoacetamide (1.1 g) is then added to the mixture which is kept far from light, and stirred for 4 hours at room temperature. After lowering the temperature to 10°C, a saturated solution of sodium bisulfite is added in order to decolorize the mixture, which is then poured into 120 ml of ice water. A product separates, which is collected by filtration, washed with water and then dried, thus obtaining 2.81 g of crude 9α-bromo-pregna-1,4-diene-11β,21-diol-3,20-dione-[17α,16α-d] -2'-methyloxazoline 21-acetate (yield 93%), MP 175°C to 176°C. An amount of 2.75 g of 9α-bromo-pregna-1,4-diene-11β,21-diol-3,20-dione-[17α,16α-d] -2'-methyloxazoline 21-acetate is dissolved under nitrogen in 137 ml of a mixture methanol:chloroform (3:2). The solution is put in ice bath and 5.5 ml of 1 N NaOH are then added within 10 minutes followed by 5.5 ml within the next 40 minutes. A strong stirring is provided for 2 hours and the temperature is kept between 0°C and 5°C, then the pH is adjusted to 7 to 8 with glacial acetic acid. The solvent is evaporated in vacuo to 20 ml of volume of solution, that is poured into ice water (130 ml). The product is collected by filtration, washed with water and dried. Yield: 1.6 g (80%), MP 221°C to 222°C. It is pregna-1,4-diene-9β,11β-epoxy-21-ol-3,20-dione-[17α,16α-d] -2'-methyloxazoline.

An amount of 1 g of the above product is dissolved in 9.4 ml of a mixture obtained by mixing 4.67 ml of hydrofluoric acid with 8.5 ml of tetrahydrofuran at the temperature of 0°C. This solution is stirred for 20 hours at the same temperature, then under strong stirring and cooling 20 ml of tetrahydrofuran are added. The solution is subsequently neutralized by the addition of 24 g of sodium bicarbonate followed by 1 g of sodium sulfate. The inorganic substance is collected and washed with ethyl acetate. The filtrate is evaporated to dryness and the product is crystallized from acetone: 0.65 g (yield 61%) of pregna-1,4-dien-9α-fluoro-11β,21-diol-3,20-dione-[17α,16α-d] -2'-methyloxazoline are obtained, MP 241°C to 244°C $[\alpha]_D$ = +83.5 (c. 0.5, $CHCl_3$). The 21-acetate has MP 252°C to 255°C $[\alpha]_D$ = +54.8 (c. 0.5, $CHCl_3$).

References

Merck Index 4028
Kleeman & Engel p. 404
DOT 12 (10) 396 (1976)
I.N. p. 428
Nathansohn, G., Winters, G. and Testa, E.; U.S. Patent 3,461,119; August 12, 1969; assigned to Lepetit S.p.A. (Italy)

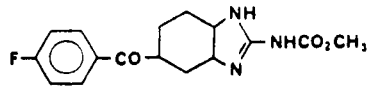
FLUBENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: Methyl-N-[5(6)-p-fluorobenzoyl-2-benzimidazolyl] carbamate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 31430-15-6

Trade Name	Manufacturer	Country	Year Introduced
Fluvermal	Janssen Le Brun	France	1980
Flubenol	Janssen	W. Germany	1982
Flumoxane	Le Brun	France	—

Raw Materials

Fluorobenzene
4-Chloro-3-nitrobenzoyl chloride
Hydrogen
S-Methylthiourea sulfate
Aluminum chloride
Ammonia
Methyl chloroformate

Manufacturing Process

To a stirred and cooled (ice bath) suspension of 25 parts of aluminum chloride in 52 parts of fluorobenzene is added dropwise a solution of 27.5 parts of 4-chloro-3-nitrobenzoyl chloride in 52 parts of fluorobenzene. Upon completion, stirring is continued overnight at room temperature. The reaction mixture is poured onto water and the product is extracted with methylene chloride. The extract is washed successively with sodium hydrogen carbonate solution and water, dried, filtered and evaporated in vacuo. The solid residue is crystallized from 2-propanol, yielding 4-chloro-4'-fluoro-3-nitrobenzophenone; MP 97.9°C.

A mixture of 24.5 parts of 4-chloro-4'-fluoro-3-nitrobenzophenone, 72 parts of methanol, 13 parts of sulfolane and 3.12 parts of ammonia is heated in a sealed tube for 20 hours at 120°C. To the reaction mixture is added successively 50 parts of water and 25 parts of a diluted hydrochloric acid solution and the whole is stirred and refluxed for 5 minutes. The reaction mixture is cooled and the precipitated product is filtered off. It is washed with 2-propanol and recrystallized from 640 parts of toluene, yielding 4-amino-4'-fluoro-3-nitrobenzophenone; MP 199°C.

A mixture of 14.5 parts of 4-amino-4'-fluoro-3-nitrobenzophenone, 160 parts of methanol,

6 parts of concentrated hydrochloric acid solution and 0.5 part of platinum oxide is hydrogenated at normal pressure and at room temperature. After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The catalyst is filtered off and the filtrate is evaporated. The residue is washed with 2-propanol and dried, yielding 3,4-diamino-4'-fluorobenzophenone hydrochloride; MP 226°C to 230.5°C.

A mixture of 8.9 parts of S-methylisothiourea sulfate, 6.05 parts of methyl chloroformate in 7 parts of water is cooled, and at a temperature of 5°C to 10°C, sodium hydroxide solution 25% is added until pH equals 8. Then there are added successively 6.4 parts of acetic acid, 2.6 parts of sodium acetate and 8.9 parts of 3,4-diamino-4'-fluorobenzophenone hydrochloride and the whole is stirred while heating at 85°C for 45 minutes (during this reaction time, water and 2-propanol is added). The precipitated product is filtered off, washed with methanol and recrystallized from a mixture of 200 parts of acetic acid and 80 parts of methanol, yielding methyl N-[5(6)-p-fluorobenzoyl-2-benzimidazolyl] carbamate; MP >260°C.

References

Merck Index 4030
DFU 3 (10) 739 (1978)
Kleeman & Engel p. 404
OCDS Vol. 2 p. 354 (1980)
DOT 16 (9) 307 (1980) & 17 (6) 259 (1981)
I.N. p. 428
Van Gelder, J.L.H., Roevens, L.F.C. and Raeymaekers, A.H.M.; U.S. Patent 3,657,267; April 18, 1972; assigned to Janssen Pharmaceutica NV

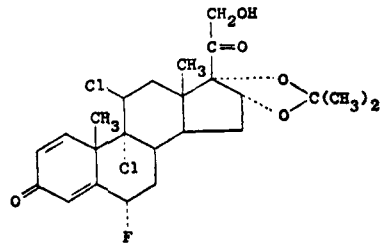
FLUCLORONIDE

Therapeutic Function: Glucocorticoid

Chemical Name: 9,11β-dichloro-6α-fluoro-21-hydroxy-16α,17[(1-methylethylidene)bis-(oxy)] -pregna-1,4-diene-3,20-dione

Common Name: Fluclorolone acetonide

Structural Formula:



Chemical Abstracts Registry No.: 3693-39-8

Trade Name	Manufacturer	Country	Year Introduced
Topilar	Syntex	U.K.	1971
Topilar	Syntex Daltan	France	1979
Gutanit	I.F.L.	Spain	—
Synemol	Syntex	—	—

Raw Materials

6α-Fluoro-16α-hydroxycortisone-21-acetate
Acetic anhydride
Methane sulfonyl chloride
Chlorine
Selenium dioxide
Potassium hydroxide
Acetone

Manufacturing Process

To 6α-fluoro-16α-hydroxy-hydrocortisone 21-acetate, described by Mills et al, *J. Am. Chem. Soc.*, volume 81, pages 1264 to 1265, March 5, 1959, there was added acetic anhydride in dry pyridine. The reaction mixture was left at room temperature overnight and was then poured with stirring into ice water. The resulting precipitate was filtered, washed with water and crystallized from acetone-hexane to give 6α-fluoro-16α-hydroxy-hydrocortisone-16α,21-diacetate. This was reacted with methane-sulfonyl chloride in dimethyl formamide in the presence of pyridine at 80°C for 1 hour. The mixture was cooled, diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and the ethyl acetate was evaporated. By recrystallization of the residue from acetone-hexane there was obtained 6α-fluoro-$\Delta^{4,9(11)}$-pregnadiene-16α,17α,21-triol-3,20-dione 16α,21 diacetate.

This was reacted with chlorine to give the dichloropregnene compound, then with selenium dioxide to give the dichloropregnadiene compound. By hydrolysis with methanolic potassium hydroxide there was obtained the free 6α-fluoro-9α,11β-dichloro-$\Delta^{1,4}$-pregnadiene-16α,-17α,21-triol-3,20-dione. By treatment with acetone in the presence of perchloric acid, the 16,17-acetonide of 6α-fluoro-9α,11β-dichloro-$\Delta^{1,4}$-pregnadiene 16α,17α,21-triol-3,20-dione was formed.

References

Merck Index 4033
Kleeman & Engel p. 405
OCDS Vol. 2 p. 198 (1980)
DOT 7 (4) 130 (1971)
I.N. p. 429
Bowers, A.; U.S. Patent 3,201,391; August 17, 1965; assigned to Syntex Corporation, Panama

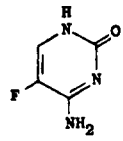
FLUCYTOSINE

Therapeutic Function: Antifungal

Chemical Name: 5-fluorocytosine

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 2022-85-7

Trade Name	Manufacturer	Country	Year Introduced
Ancobon	Roche	U.S.	1972
Ancotil	Roche	France	1974
Alcobon	Roche	U.K.	1974
Ancotil	Roche	W. Germany	1975
Ancotil	Roche	Japan	1979
Ancotil	Roche	Italy	1982

Raw Materials

5-Fluorouracil
Hydrogen chloride
Phosphorus oxychloride
Ammonia

Manufacturing Process

The preparation of 5-fluorouracil is given under "Fluorouracil." As described in U.S. Patent 3,040,026, 5-fluorouracil is then subjected to the following steps to give flucytosine.

Step 1: 2,4-Dichloro-5-Fluoropyrimidine – A mixture of 104 grams (0.8 mol) of 5-fluorouracil, 1,472 grams (9.6 mols) of phosphorus oxychloride and 166 grams (1.37 mols) of dimethylaniline was stirred under reflux for 2 hours. After cooling to room temperature, phosphorus oxychloride was removed by distillation at 18 to 22 mm and 22° to 37°C. The residue was then poured into a vigorously stirred mixture of 500 ml of ether and 500 gram of ice. After separating the ether layer, the aqueous layer was extracted with 500 ml, then 200 ml of ether. The combined ether fractions were dried over sodium sulfate, filtered, and the ether removed by vacuum distillation at 10° to 22°C. The residue, a yellow solid melting at 37° to 38°C, weighed 120 grams corresponding to a 90% yield. Vacuum distillation of 115 grams of this material at 74° to 80°C (16 mm) gave 108 grams of white solid melting at 38° to 39°C corresponding to an 84.5% yield.

Step 2: 2-Chloro-4-Amino-5-Fluoropyrimidine – To a solution of 10.0 grams (0.06 mol) of 2,4-dichloro-5-fluoropyrimidine in 100 ml of ethanol, 25 ml of concentrated aqueous ammonia were slowly added. A slightly opalescent solution resulted. The temperature gradually rose to 35°C. The solution was then cooled in ice to 18°C and thereafter remained below 30°C. After three hours, a Volhard titration showed that 0.0545 mol of chlorine was present in ionic form. Storage in a refrigerator overnight resulted in some crystallization of ammonium chloride. A white sludge, resulting from the evaporation of the reaction mixture at 40°C, was slurried with 75 ml of water, filtered and washed free of chloride. After drying in vacuo, the product melted at 196.5° to 197.5°C, yield 6.44 grams. Evaporation of the mother liquors yielded a second crop of 0.38 gram, raising the total yield to 6.82 grams (79.3%).

Step 3: 5-Fluorocytosine – A slurry of 34.0 grams (0.231 mol) of 2-chloro-4-amino-5-fluoropyrimidine in 231 ml of concentrated hydrochloric acid was heated in a water bath at 93° to 95°C for 125 minutes. The reaction was followed by means of ultraviolet spectrophotometry using the absorption at 245, 285, and 300 mμ as a guide. The absorption at 300 mμ rose to a maximum after 120 minutes and then dropped slightly. The clear solution was cooled to 25°C in an ice bath, then evaporated to dryness under vacuum at 40°C. After slurrying with water three times and reevaporating, the residue was dissolved in 100 milliliters of water. To this solution, cooled in ice, 29 ml of concentrated ammonia were added dropwise. The resulting precipitate was filtered, washed free of chloride with water, then with alcohol and ether. After drying in vacuo at 65°C, the product weighed 22.3 grams. An additional 6.35 grams was obtained by evaporation of the mother liquor, thus yielding a total of 28.65 grams (96.0%).

References

Merck Index 4035

Kleeman & Engel p. 406
PDR p. 1472
DOT 8 (11) 418 (1972)
I.N. p. 429
REM p. 1227
Heidelberger, C. and Duschinsky, R.; U.S. Patent 2,802,005; August 6, 1957
Duschinsky, R. and Heidelberger, C.; U.S. Patent 2,945,038; July 12, 1960; assigned to Hoffmann-La Roche Inc.
Duschinsky, R.; U.S. Patent 3,040,026; June 19, 1962; assigned to Hoffmann-La Roche Inc.
Berger, J. and Duschinsky, R.; U.S. Patent 3,368,938; February 13, 1968; assigned to Hoffmann-La Roche Inc.

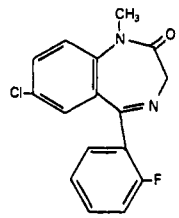
FLUDIAZEPAM HYDROCHLORIDE

Therapeutic Function: Anxiolytic

Chemical Name: 1-Methyl-7-chloro-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one hydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 3900-31-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Erispan	Sumitomo	Japan	1981

Raw Materials

2-Aminomethyl-1-methyl-5-chloro-3(o-fluorophenyl)indole HCl
Chromic anhydride
Ammonia
Hydrogen chloride

Manufacturing Process

A solution of 60 g of chromic anhydride in 40 ml of water was added dropwise to a suspension of 60 g of 2-aminomethyl-1-methyl-5-chloro-3-(o-fluorophenyl)-indole hydrochloride in 600 ml of acetic acid. The mixture was stirred at room temperature overnight. To the reaction mixture was added 1.1 liters of ether and 1 liter of water and then 800 ml of 28% ammonium hydroxide, in small portions. The ethereal layer separated, washed with water, dried, and concentrated under reduced pressure. The residue (51.8 g) was dissolved in 100 ml of ethanol, and 100 ml of 20% ethanolic hydrogen chloride was added to the solution and the mixture was cooled. The precipitate was collected by filtration to yield 46.5 g of 1-methyl-7-chloro-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one hydrochloride, melt-

ing point 218°C (decomposed). Recrystallization from ethanol raised the melting point to 218.5°C to 219°C (decomposed).

References

Merck Index 4036
DFU 6 (12) 774 (1981)
DOT 18 (2) 68 (1982)
I.N. p. 430
Yamamato, H., Inaba, S., Okamoto, T., Hirohashi, T., Ishizumi, K., Yamamoto, M., Maruyama, I., Mori, K. and Kobayashi, T.; U.S. Patents 3,723,461; March 27, 1973; 3,828,027; August 6, 1974 and 3,925,364; December 9, 1975; all assigned to Sumitomo Chemical Co., Ltd.

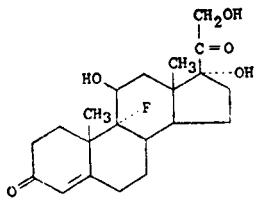
FLUDROCORTISONE ACETATE

Therapeutic Function: Antiinflammatory

Chemical Name: 9-fluoro-11β,17,21-trihydroxy-pregn-4-ene-3,20-dione acetate

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 514-36-3; 127-31-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alflorone Acetate	MSD	U.S.	1954
Florinef Acetate	Squibb	U.S.	1955
F-Cortef Acetate	Upjohn	U.S.	1955
Alfa-Fluorone	Ausonia	Italy	—
Alfanonidrone	Difer	Italy	—
Astonin	Merck	W. Germany	—
Blephaseptyl	Chauvin-Blache	France	—
Cortineff	Polfa	Poland	—
Florotic	Squibb	U.S.	—
Fludrocortone	MSD	—	—
Myconef	Squibb	U.S.	—
Panotile	Inpharzam	W. Germany	—
Panotile	Arsac	France	—
Schlerofluron	Schering	W. Germany	—

Raw Materials

Hydrocortisone acetate
Hypobromous acid
Phosphorus oxychloride
Hydrogen fluoride

Manufacturing Process

Hydrocortisone acetate is first reacted with phosphorus oxychloride in pyridine to give the

corresponding olefin. Then a sequence consisting of hypobromous acid addition, ring closure to the epoxide and ring opening with hydrogen fluoride gives fludrocortisone acetate. Preparation of a crystalline product is described then in U.S. Patent 2,957,013.

References

Merck Index 4037
Kleeman & Engel p. 407
OCDS Vol. 1 p. 192 (1977)
DOT 7 (6) 203 (1971)
I.N. p. 430
REM p. 965
Graber, R.P. and Snoddy, C.S. Jr.; U.S. Patent 2,957,013; October 18, 1960; assigned to Merck & Co., Inc.

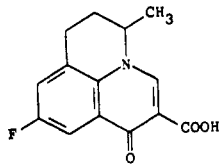
FLUMEQUINE

Therapeutic Function: Antibacterial

Chemical Name: 9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 42385-25-6

Trade Name	Manufacturer	Country	Year Introduced
Apurone	Riker	France	1977
Uribact	Diethelm	Switz.	1983
Flumural	Spa	Italy	—

Raw Materials

6-Fluoro-2-methyltetrahydroquinoline
Diethyl ethoxymethylenemalonate
Polyphosphoric acid
Sodium hydroxide

Manufacturing Process

6-Fluoro-2-methyltetrahydroquinoline (32.2 g, 0.2 mol) is mixed with diethyl ethoxymethylenemalonate, and the mixture is heated at 125°C to 130°C for 3 hours. Polyphosphoric acid (200 g) is added, and the solution is gradually heated to 115°C to 120°C in an oil bath with occasional stirring. The temperature is maintained for 1 hour, then the mixture is poured into 600 ml of water and neutralized with 40% sodium hydroxide solution. The product ester which precipitates is separated by filtration, washed with water and suspended in 2 liters of 10% sodium hydroxide solution. The mixture is heated on the steam bath for 1 hour, treated

with decolorizing charcoal, filtered, then neutralized with concentrated hydrochloric acid. The solid product is isolated by filtration of the hot solution, washed with water and recrystallized from dimethylformamide.

References

Merck Index 4041
Kleeman & Engel p. 411
OCDS Vol. 3 p. 186 (1984)
DOT 11 (10) 410 & 14 (8) 365 (1978)
I.N. p. 431
Gerster, J.F.; U.S. Patent 3,896,131; July 22, 1975; assigned to Riker Laboratories, Inc.

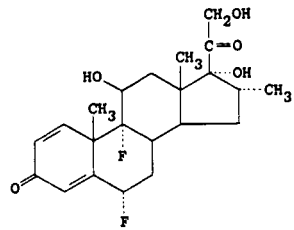
FLUMETHASONE

Therapeutic Function: Glucocorticoid; antiinflammatory

Chemical Name: 6,9-Difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione

Common Name: 6α-Fluorodexamethasone

Structural Formula:



Chemical Abstracts Registry No.: 2135-17-3

Trade Name	Manufacturer	Country	Year Introduced
Locacorten	Ciba	W. Germany	1964
Locorten	Ciba	Italy	1965
Locorten	Ciba	U.K.	1965
Locorten	Ciba-Geigy	Japan	1970
Locorten	Ciba-Geigy	U.S.	1970
Cerson	VEB Leipziger	E. Germany	—
Loriden	Polfa	Poland	—
Topicorten	Trima	Israel	—

Raw Materials

6α-Fluoro-9β,11β-epoxy-16α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate
Hydrogen fluoride

Manufacturing Process

To approximately 1.3 g of hydrogen fluoride contained in a polyethylene bottle and maintained at -60°C was added 2.3 ml of tetrahydrofuran and then a solution of 500 mg (0.0012 mol) of 6α-fluoro-9β,11β-epoxy-16α-methyl-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione

21-acetate in 2 ml of methylene chloride. The steroid solution was rinsed in with an additional 1 ml of methylene chloride. The light red colored solution was then kept at approximately -30°C for 1 hour and at -10°C for 2 hours. At the end of this period it was mixed cautiously with an excess of cold sodium bicarbonate solution and the organic material extracted with the aid of additional methylene chloride. The combined extracts were washed with water, dried over anhydrous sodium sulfate and concentrated to approximately 35 ml. The solution was chromatographed over 130 g of Florisil anhydrous magnesium silicate. The column was developed with 260 ml portions of hexanes (Skellysolve B) containing increasing proportions of acetone. There was thus eluted 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-acetate which was freed of solvent by evaporation of the eluate fractions.

References

Merck Index 4042
Kleeman & Engel p. 411
OCDS Vol. 1 p. 200 (1977)
I.N. p. 431
REM p. 965
Lincoln, F.H., Schneider, W.P. and Spero, G.B.; U.S. Patent 3,557,158; January 19, 1971; assigned to The Upjohn Co.

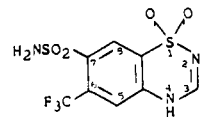
FLUMETHIAZIDE

Therapeutic Function: Carbonic anhydrase inhibitor

Chemical Name: 6-(Trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: Trifluoromethylthiazide

Structural Formula:



Chemical Abstracts Registry No.: 148-56-1

Trade Name	Manufacturer	Country	Year Introduced
Ademol	Squibb	U.S.	1959

Raw Materials

3-Trifluoromethylaniline
Ammonia
Chlorosulfonic acid
Formic acid

Manufacturing Process

Chilled 3-trifluoromethylaniline (32.2 g) is added dropwise over a 45-minute period to 150 ml of chlorosulfonic acid with stirring and cooling. The ice bath is removed and 140 g of sodium chloride is added over 3 hours. The mixture is heated on a water bath for 30 minutes, then gradually up to 160°C over 6 hours. The cooled reaction mixture is diluted with 500 ml of an ice water slurry and taken into ether. The ether is dried and evaporated to leave 5-trifluoromethylamine-2,4-disulfonyl chloride.

The crude residue is heated on the steam bath for 1 hour with 75 ml of concentrated ammonium

hydroxide. Cooling and filtration gives 2,4-disulfamyl-5-trifluoromethylaniline, MP 241°C to 243°C.

This intermediate is treated with an excess of 98% formic acid at steam bath temperature for 3 hours. Evaporation and dilution with water gives 7-sulfamyl-6-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide, MP 304°C to 308°C.

References

Merck Index 4043
OCDS Vol. 1 p. 355 (1977) & 2 p. 355 (1980)
I.N. p. 431
Smith Kline & French Laboratories; British Patent 861,809; March 1, 1961

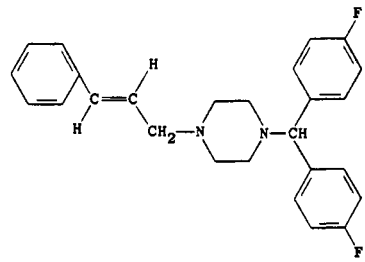
FLUNARIZINE HCl

Therapeutic Function: Vasodilator

Chemical Name: 1-[Bis(4-fluorophenyl)methyl]-4(3-phenyl-2-propenyl)piperazine

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 30484-77-6; 52468-60-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sibelium	Janssen	W. Germany	1977
Sibelium	Janssen	Switz.	1980
Issium	Farmochimica	Italy	1981
Fluxarten	Zambeletti	Italy	1981
Dinaplex	Sidus	Argentina	–
Flugeral	Italfarmaco	Italy	–
Flunagen	Gentili	Italy	–
Gradient Polifarma	Polifarma	Italy	–
Mondus	Labinca	Argentina	–

Raw Materials

Di-(p-Fluorophenyl)chloromethane
1-Cinnamylpiperazine
Sodium carbonate

Manufacturing Process

A mixture of 14.3 parts of di-(p-fluorophenyl)-chloromethane, 10.1 parts of 1-cinnamylpiperazine, 12.7 parts of sodium carbonate, a few crystals of potassium iodide in 200 parts of 4-methyl-2-pentanone is stirred and refluxed for 21 hours. The reaction mixture is cooled

and 50 parts of water are added. The organic layer is separated, dried, filtered and evaporated. The oily residue is dissolved in 480 parts of anhydrous diisopropyl ether. This solution is boiled with activated charcoal, filtered and to the clear filtrate is added an excess of 2-propanol, previously saturated with gaseous hydrogen chloride. The precipitated salt is filtered off and recrystallized from a mixture of 2-propanol and ethanol, yielding 1-cinnamyl-4-(di-p-fluorobenzhydryl)piperazine dihydrochloride, MP 251.5°C.

References

Merck Index 4045
Kleeman & Engel p. 412
OCDS Vol. 2 p. 31 (1980)
DOT 14 (3) 109 (1978)
I.N. p. 432
Janssen, P.A.J.; U.S. Patent 3,773,939; November 20, 1973; assigned to Janssen Pharmaceutica N.V.

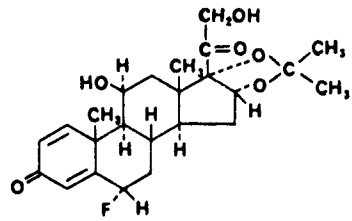
FLUNISOLIDE

Therapeutic Function: Antiinflammatory

Chemical Name: 16α,17α-Isopropylidenedioxy-6α-fluoro-1,4-pregnadiene-11β,21-diol-3,20-dione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3385-03-3

Trade Name	Manufacturer	Country	Year Introduced
Syntaris	Syntex	U.K.	1978
Syntaris	Syntex	W. Germany	1979
Syntaris	Syntex	Switz.	1980
Nasalide	Syntex	U.S.	1981
Syntaris	Recordati	Italy	1982
Lunis	Valeas	Italy	1983
Aero Bid	Key	U.S.	–
Bronalide	Krewel	W. Germany	–
Lobilan Nasal	Astra	–	–
Lokilan Nasal	Syntex	–	–
Rhinalar	Syntex	–	–

Raw Materials

6α-Fluoroprednisolone
Bacterium *Streptomyces roseochromogenus*
Acetone
Perchloric acid

Manufacturing Process

(a) Preparation of 6α-fluoro-16α-hydroxyprednisolone: 1.9 liters of whole mash containing 400 mg of 6α-fluoroprednisolone (6α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione) acted upon by *Streptomyces roseochromogenus* AE-751 (or Waksman No. 3689) is filtered and the filtrate extracted three times with 2 liter portions of ethyl acetate. The mycelium is extracted with 500 ml of ethyl acetate and the mixture filtered. The combined ethyl acetate extracts are washed with 200 ml of water and concentrated to a residue. The residue is subjected to partition chromatograph using a 200 g column of diatomaceous earth moistened with the lower phase of an equilibrated solvent system composed of 1 volume of water, 5 volumes of dioxane, and 3 volumes of cyclohexane. The upper phase is used to develop the column and the activity of the eluent is followed by measuring the ultraviolet absorbance at 240 mμ. The cuts containing most of the activity are concentrated to a syrupy residue and triturated with acetone. Crystals (25 mg) form and recrystallization gives a product with a MP of 226°C to 230°C.

(b) Preparation of 16α,17α-isopropylidenedioxy-6α-fluoro-1,4-pregnadiene-11β,21-diol-3,20-dione: 15 mg of crystalline 6α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione [6α-fluoro-16α-hydroxyprednisolone described in U.S. Patent 2,838,546 and prepared as described in (a) above] is dissolved in 2 ml of acetone and 0.02 ml of 70% perchloric acid is added. The solution is allowed to stand 1 hour. Then 0.5 ml of saturated sodium bicarbonate solution is added and the solution concentrated under reduced pressure to about 1 ml. The solution is allowed to stand overnight and the crystals which form are filtered, washed with ether and recrystallized from acetone-hexane. The crystals are the 16α,17α-isopropylidene derivative of 6α-fluoro-16α-hydroxyprednisolone.

References

Merck Index 4046
DFU 3 (2) 81 (1979)
Kleeman & Engel p. 413
PDR pp. 966, 1803
OCDS Vol. 2 p. 181 (1980)
DOT 16 (8) 252 (1980)
I.N. p. 432
REM p. 972
American Cyanamid Co.; British Patent 933,867; August 14, 1963

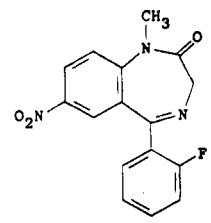
FLUNITRAZEPAM

Therapeutic Function: Hypnotic

Chemical Name: 5-(2-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepin-2-one

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 1622-62-4

Trade Name	Manufacturer	Country	Year Introduced
Roipnol	Roche	Italy	1976
Rohypnol	Roche	France	1978
Rohypnol	Roche	W. Germany	1979
Rohypnol	Sauter	U.K.	1982
Hypnodorm	Teva	Israel	—
Hipnosedon	Roche	—	—
Narcozep	Roche	France	—

Raw Materials

p-Chloroaniline
o-Fluorobenzoyl chloride
Ammonia
Sulfuric acid
Methyl iodide
Hydrogen
Bromoacetyl bromide
Potassium nitrate
Sodium hydride

Manufacturing Process

A mixture of 176 grams of orthofluorobenzoyl chloride and 64 grams of para-chloroaniline was stirred and heated to 180°C, at which temperature 87 grams of zinc chloride was introduced, the temperature raised to 200° to 205°C and maintained there for 40 minutes. The golden colored melt was quenched by the careful addition of 500 ml of 3 N hydrochloric acid and the resulting mixture refluxed for 5 minutes. The acid solution was decanted and the process repeated three times to remove all orthofluorobenzoic acid. The grey granular residue was dissolved in 300 ml of 75% (v/v) sulfuric acid and refluxed for 40 minutes to complete hydrolysis. The hot solution was poured over 1 kg of ice and diluted to 2 liters with water. The organic material was extracted with four 300 ml portions of methylene chloride, and the combined extracts subsequently washed with two 500 ml portions of 3 N hydrochloric acid to remove traces of para-chloroaniline, three 500 ml portions of 5 N sodium hydroxide solution to remove orthofluorobenzoic acid, and finally two 200 ml portions of saturated brine solution.

The combined methylene chloride extracts were dried over anhydrous sodium sulfate and the solvent removed to give the crude 2-amino-5-chloro-2'-fluorobenzophenone which upon recrystallization from methanol formed yellow needles melting at 94° to 95°C.

50.0 grams of 2-amino-5-chloro-2'-fluorobenzophenone in 300 cc of tetrahydrofuran was hydrogenated at atmospheric pressure in the presence of 10 grams of charcoal (Norite), 30.0 grams of potassium acetate and 2.5 cc of a 20% palladous chloride solution (20% by weight of palladium). After an initiation period varying from 10 minutes to an hour, hydrogen uptake was rapid and stopped completely after the absorption of the theoretical amount.

Filtration of the catalyst over a Hyflo pad and removal of the solvent left a yellow crystalline residue. The crude mixture of ketone and potassium acetate was partitioned between methylene chloride (300 cc) and water (1 liter). The layers were separated and the water layer washed with methylene chloride (3 x 50 cc). The organic layers were combined, washed with 3 N sodium hydroxide solution (2 x 50 cc), water (3 x 100 cc), dried over anhydrous sodium sulfate and filtered. The solvent was removed and the product recrystallized from ethanol to give 2-amino-2'-fluorobenzophenone as yellow prisms melting at 126° to 128°C.

A solution of 21.5 grams of 2-amino-2'-fluorobenzophenone in 500 cc of ether was treated with 20 cc of a 20% (v/v) solution of bromoacetyl bromide in ether. The mixture was shaken and allowed to stand for 5 minutes and then washed with water (20 cc). The proc-

ess was repeated five times. The final solution was washed thoroughly with water (5 x 500 cc) and concentrated to 100 cc. The crystals were filtered and recrystallized from methanol to give 2-bromacetamido-2'-fluorobenzophenone as white needles melting at 117° to 118.5°C.

A solution of 23.7 grams of 2-bromoacetamido-2'-fluorobenzophenone in tetrahydrofuran (100 cc) was added to liquid ammonia (approximately 500 cc) and allowed to evaporate overnight. The residue was treated with water (1 liter) and the crystals filtered off and refluxed in toluene (100 cc) for 30 minutes. The mixture was treated with decolorizing carbon (Norite) and filtered over Hyflo. The solution was concentrated to a small volume (25 cc) cooled, diluted with 20 cc of ether and allowed to stand. The product was recrystallized from acetone/hexane to give 5-(2-fluorophenyl)3H-1,4-benzodiazepin-2(1H)-one as white needles melting at 180° to 181°C.

23.8 grams of 5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one was dissolved in 50 cc of concentrated sulfuric acid at 0°C. To the resulting mixture there was then added dropwise with stirring a solution of 7.1 grams of potassium nitrate in 20 cc of concentrated sulfuric acid. The mixture was stirred for 2½ hours at 0°C and then diluted with 300 grams of ice. The resulting solution was made alkaline with concentrated ammonium hydroxide solution, keeping the temperature at 0°C. The formed suspension was extracted thoroughly with methylene chloride (6 x 100 cc). The organic layers were combined, washed with saturated brine solution, dried over anhydrous sodium sulfate and filtered. Removal of the solvent yielded a brown gum which was taken up in a small amount of methylene chloride and filtered through a pad of grade I alumina. The alumina was eluted with methylene chloride, the solvent removed, and the residue crystallized from acetone/hexane to yield 7-nitro-5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one as white needles melting at 210° to 211°C.

20.2 grams of the abovementioned 7-nitro-5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one was dissolved in 60 cc of N,N-dimethyl formamide to which was then added 3.49 grams of a 50% suspension of sodium hydride in heavy mineral oil. The mixture was allowed to stir for 15 minutes in the cold, 11.2 grams of methyl iodide was added and the solution was stirred for a further 20 minutes. Solvent was removed under reduced pressure to give an oil which was partitioned between water and methylene chloride (1 liter/300 cc), the water layer was extracted with methylene chloride (5 x 200 cc), the organic layers combined and washed with water (2 x 100 cc), 3N hydrochloric acid (1 x 50 cc), water (3 x 100 cc), dried over anhydrous sodium sulfate and filtered.

Removal of the solvent gave an oil which was taken up in ether and filtered through a pad of Woelm grade I alumina. The eluent was concentrated and the residue was crystallized from methylene chloride/hexane yielding 1-methyl-7-nitro-5-(2-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one as pale yellow needles melting at 166° to 167°C.

References

Merck Index 4047
Kleeman & Engel p. 413
OCDS Vol. 2 p. 406 (1980)
DOT 11 (5) pp. 177,211 (1975) & 19 (3) p. 163 (1983)
I.N. p. 432
REM p. 1064
Kariss, J. and Newmark, H.L.; U.S. Patent 3,116,203; December 31, 1963; assigned to Hoffmann-La Roche Inc.
Kariss, J. and Newmark, H.L.; U.S. Patent 3,123,529; March 3, 1964; assigned to Hoffmann-La Roche Inc.
Keiler, O., Steiger, N. and Sternbach, L.H.; U.S. Patent 3,203,990; August 31, 1965; assigned to Hoffmann-La Roche Inc.