IBUPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: α-Methyl-4-(2-methylpropyl)benzene acetic acid

Common Name: 2-(4-Isobutylphenyl)propionic acid

Structural Formula:

Chemical Abstracts Registry No.: 15687-27-1

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**Raw Materials**

- Sulfur
- Isobutylbenzene
- Sodium
- Sodium hydroxide
- Ethyl iodide
- Acetyl chloride
- Ethanol
- Ethyl carbonate

**Manufacturing Process**

Isobutylbenzene is first acetylated to give isobutylacetophenone. 4-i-butyacetophenone (40 g), sulfur (11 g) and morpholine (30 ml) were refluxed for 16 hours, cooled, acetic acid (170 ml) and concentrated hydrochloric acid (280 ml) were added and the mixture was refluxed for a further 7 hours. The
mixture was concentrated in vacuo to remove acetic acid and the concentrate was diluted with water.

The oil which separated was isolated with ether, the ethereal solution was extracted with aqueous sodium carbonate and this extract was acidified with hydrochloric acid. The oil was isolated with ether, evaporated to dryness and the residue was esterified by refluxing with ethanol (100 ml) and concentrated sulfuric acid (3 ml) for 5 hours. The excess alcohol was distilled off, the residue was diluted with water, and the oil which separated was isolated with ether. The ethereal solution was washed with sodium carbonate solution; then with water and was dried. The ether was evaporated off and the oil was distilled to give ethyl 4-i-butylphenylacetate.

Sodium ethoxide from sodium (3.67 g) in absolute alcohol (64 ml) was added over 20 minutes with stirring to a mixture of ethyl 4-i-butylphenylacetate (28.14 g) and ethyl carbonate (102 ml) at 100°C. The reaction flask was fitted with a Fenske column through which alcohol and then ethyl carbonate distilled. After 1 hour when the still head reached 124°C heating was discontinued. Glacial acetic acid (12 ml) and water (50 ml) was added to the stirred ice-cooled mixture and the ester isolated in ether, washed with sodium carbonate solution, water and distilled to give ethyl 4-i-butylphenylmalonate.

Ethyl 4-i-butylphenylmalonate (27.53 g) in absolute alcohol (25 ml) was added with stirring to a solution of sodium ethoxide from sodium (2.17 g) in absolute alcohol (75 ml). Ethyl iodide (15 ml) was added and the mixture refluxed for 2% hours, the alcohol distilled and the residue diluted with water, extracted with ether, washed with sodium bisulfite, water, and evaporated to dryness.

The residual oil was stirred and refluxed with sodium hydroxide (75 ml of 5 N), water (45 ml) and 95% ethanol (120 ml). Within a few minutes a sodium salt separated and after 1 hour the solid was collected, washed with ethanol, dissolved in hot water and acidified with dilute hydrochloric acid to give the methyl malonic acid which was collected and dried in vacuo MP 177° to 180°C (dec.).

The malonic acid (9 g) was heated to 210° to 220°C in an oil bath for 20 minutes until decarboxylation had ceased. The propionic acid was cooled and recrystallized from light petroleum (BP 60° to 80°C). Two further recrystallizations from the same solvent gave colorless prisms of 2-(4-isobutylphenyl)propionicacid MP 75° to 77.5°C. (The procedure was reported in US Patent 3,228,831.)

References

Merck Index 4797
Kleeman and Engel p. 482
PDR pp. 687, 728, 830, 1854, 1897
DOT 5 (3) 101 (1969)
I.N. p. 510
REM p. 1117
IBUPROXAM

**Therapeutic Function:** Antiinflammatory

**Chemical Name:** N-Hydroxy-α-ethyl-4-(2-methylpropyl)benzene-acetamide

**Common Name:** -

**Structural Formula:**

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H\(\text{O}\)\(\text{N}\)
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**Chemical Abstracts Registry No.:** 53648-05-8

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**Raw Materials**

- 2-(4-Isobutylphenyl)propionic acid
- Hydroxylamine hydrochloride
- Ethanol
- Potassium hydroxide

**Manufacturing Process**

In a 1,000 ml three-necked flask equipped with a stirrer, a dropping funnel and a silica gel guard pipe, 46.7 g hydroxylamine hydrochloride are dissolved cold in 480 ml methanol. Separately a solution of 56.1 g KOH in 280 ml methanol is prepared, heated to 30°C and admixed, dropwise under stirring to the hydroxylamine solution. All successive temperature increases during this admixture are prevented by cooling in an ice bath. After the whole KOH solution has been admixed, the mixture is left standing for 5 minutes so as to attain the complete precipitation of the KCl.

Separately, 72.02 g ethyl 2-(4-isobutylphenyl)-propionate, obtained by the esterification of 2-(4-isobutylphenyl)-propionic acid with ethanol and concentrated H\(_2\)SO\(_4\), are solved with 100 ml methanol, this solution is introduced drop by drop into the reaction flask, and stirred and cooled for 5
hours on an ice bath. Thereafter it is suction filtered, the residue is washed with all together 50 ml methanol, the wash is added to the filtrate, thereafter the whole is evaporated in a water bath with a rotating evaporator at a reduced pressure, until 100-200 ml of a concentrated solution are obtained. This solution is poured into a 200 ml beaker into which are stirred approximately 1,000 ml 1.25N acetic acid. This mixture is left standing for 24 hours, thereafter suction filtered. The resulting filtrate is taken up with 100 ml petroleum ether at 40°C to 60°C, in order to solve any possible residue of unreacted starting ester, and refiltered. Approximately 50g of 2-(4-isobutylphenyl)-propiohydroxamic acid are obtained, having a melting point of 119°C to 121°C on Kofler's hot stage.

References

Merck Index 4798
DFU 2 (12) 808 (1977)
I.N. p. 511

IBUTILIDE FUMARATE

Therapeutic Function: Antiarrhythmic

Chemical Name: Methanesulfonamide, N-(4-(4-(ethylheptylamino)-1-hydroxybutyl)phenyl)-, (2E)-2-butenedioate (2:1) (salt)

Common Name: Ibutilide fumarate

Structural Formula:

![Structural Formula](image)

Chemical Abstracts Registry No.: 122647-32-9; 122647-31-8 (Base)

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Raw Materials

Aniline

Methanesulfonyl chloride
Manufacturing Process

A mechanically stirred solution of aniline (139.7 g, 1.5 mole) in pyridine (2 L), under N₂ is cooled in an ice bath. Methanesulfonyl chloride (171.8 g, 1.5 mole) is added dropwise to this solution while the temperature is maintained at 15°-20°C, which results in a red-orange color change in the reaction mixture. After the addition is complete the ice bath is removed and the reaction is allowed to continue at room temperature. The reaction is complete after 2.5 h. The reaction mixture is concentrated in vacuo and the residue is combined with 700 ml of water which results in crystallization of a dark red material.

This material is filtered and washed several times with water. The filtered material is dissolved in CH₂Cl₂, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue is dissolved in hot ethyl acetate, treated with Darco (decolorizing carbon) and crystallized to yield methanesulfonanilide which had a melting point: 93°-94°C.

A mechanically stirred suspension of aluminum chloride (88.0 g, 0.66 moles) and 150 ml of carbon disulfide under N₂ is cooled in an ice bath. Methanesulfonanilide (30.0 g, 0.175 mol) and succinic anhydride (17.5 g, 0.175 mol) are combined and added rapidly to the cooled reaction mixture. The ice bath is removed and the mixture is stirred at room temperature for 6 h. The reaction mixture is then heated to 55°C and allowed to continue for 18 h. The reaction mixture is separated into two layers the bottom of which solidifies.

The upper layer is decanted and the remaining solid layer is decomposed with ice. The resulting suspension is filtered and the solid is washed several times with methylene chloride and dissolved in a mixture of saturated sodium bicarbonate (500 ml) and water (500 ml). This solution is acidified (pH 2) with HCl and the resulting precipitate is collected by filtration, redissolved in NaHCO₃ and reprcipitated with HCl. The solid, 4-[(methylsulfonyl)amino]-γ-oxobenzenebutanoic acid, is collected by filtration. Melting point 198°-200°C.

A stirred solution of 4-[(methylsulfonyl)amino]-γ-oxobenzenebutanoic acid (12.0 g, 0.044 mol) in DMF (100 ml) under N₂ is cooled in an ice bath to 5°C and treated with 1-hydroxybenzotriazole (5.94 g, 0.044 mol) and N,N'-dicyclohexylcarbodiimide (9.08 g, 0.044 mol). After 1 hour, ethylheptylamine (6.3 g, 0.044 mol) is added, after an additional 30 min the ice bath is removed and the mixture is kept at room temperature for 18 h.

The reaction mixture is filtered over a Celite filter aid and the filtrate is concentrated under vacuum. The resulting material is dissolved in CH₂Cl₂, washed with dilute HCl, NaHCO₃ and concentrated. The residue is chromatographed over silica gel (1.25 kg) with 5% MeOH : 1% NH₄OH : CH₂Cl₂. The N-ethyl-N-heptyl-γ-oxo-4-[(methylsulfonyl)amino]
benzenebutanamide thus obtained is crystallized from EtOAc to yield 10.77 g, melting point 100°-102°C.

To a N₂ covered suspension of 0.29 g (7.57 mmol) of LiAlH₄ in 10 ml of THF cooled in an ice bath is added a solution of 1.0 g (2.52 mmol) of N-ethyl-N-heptyl-γ-oxo-4-[methylsulfonyl]amino]benzenebutanamide in 10 ml of THF over 6 min. The ice bath is then removed and the mixture heated at reflux for 27 h and then stirred at room temperature for 2 days. The mixture is cooled in an ice bath and there is added dropwise 10 ml of aqueous sodium potassium tartrate followed by EtOAc and H₂O to keep the mixture fluid. The aqueous fraction is extracted once with EtOAc and the combined EtOAc fractions are washed in turn with H₂O and concentrated in vacuo. The residue is chromatographed on a 200 ml silica gel column (elution with 6% MeOH : CH₂Cl₂ containing 0.5% NH₄OH) and 9.7 ml fractions were collected and treated with Et₂O and aqueous NaHCO₃. The organic layer is concentrated in vacuo to yield N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl] methanesulfonamide.

Preparation of fumarate (WO Patent 01/07417). To dichloromethane solution of 4-[4-N-[(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide is added hemimolar quantities of fumaric acid and heated to reflux until a clear solution was obtained. Upon cooling the fumarate of 4-[4-N-[(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide was obtained.

References

Jackson B.H., Jr.; US Patent No. 5,155,268; Oct. 13, 1992; Assigned: The Upjohn Company (Kalamazoo, MI)

***

**IDOXURIDINE**

**Therapeutic Function:** Antiviral (ophthalmic)

**Chemical Name:** 2'-Deoxy-5-iodouridine

**Common Name:** -

**Structural Formula:**

![Structural formula of Idoxuridine](image)
Chemical Abstracts Registry No.: 54-42-2

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Raw Materials

5-Iodouracil  3,5-Di-p-tolyl-desoxy-D-ribofuranosyl chloride
Acetic anhydride
Acetic acid  Sodium hydroxide

Manufacturing Process

5 g of 5-ido-uracil (obtained according to T.B. Johnson et al., J. Biol. Chem. 1905/6, 1, 310) in 15 cc of acetic anhydride are heated under reflux for 4.5 hours. The acetylated derivative crystallizes on cooling. The crystallized product is chilled for ½ hour then filtered with suction, washed with acetic anhydride and then with ether and dried. 4.5 g of 1-acetyl-5-ido-uracil, MP 167°C, are thus obtained.

1.51 g of mercuric acetate is dissolved in 50 cc of methanol under reflux and 1.35 g of 1-acetyl-5-ido-uracil are added. A white precipitate is soon formed. The reaction mixture is kept under reflux for % hour and then allowed to cool
to room temperature. The precipitate is then filtered with suction, washed with methanol and dried.

2.1 g of monomericurc 5-iodo-uracil, MP 280°C, are thus obtained as a colorless powder, insoluble in water and the majority of the usual organic solvents, such as benzene, chloroform, alcohol, ether and acetone.

1.46 g of 5-iodo-uracil monomericurc derivative are introduced into 50 cc of chloroform and 20 to 30 cc of the solvent are distilled off under normal pressure to ensure good dehydration of the reaction medium. The mixture is cooled to room temperature and 2.59 g of 3,5-di-p-tolyl-desoxy-D-ribofuranosyl chloride added. The mixture is agitated for 6 hours with glass balls, filtered, rinsed with chloroform and the filtrate is successively washed with an aqueous sodium iodide solution, with water, with a saturated solution of sodium bicarbonate and again with water. The product is dried over sodium sulfate, filtered and evaporated to dryness.

The residue crystallizes in ether and yields about 600 mg of β-3',5'-di-p-tolyl-2'-desoxy-5-iodo-uridine which is recrystallized from toluene. The product is obtained as colorless crystals, soluble in chloroform and pyridine, sparingly soluble in acetone, benzene ether and alcohol, insoluble in water, MP 193°C.

206 mg of 3',5'-di-p-tolyl-2'-desoxy-5-iodo-uridine are heated at 80°C with 2.5 cc of caustic soda solution (0.4 N) for ½ hour. The solution obtained is cooled, filtered and then acidified with acetic acid. The desoxy-iodo-uridine and the p-toluic acid crystallize. Ether is added to dissolve the p-toluic acid, the mixture is chilled, filtered with suction, washed with water and ether, and dried. The residue is recrystallized from water and 100 mg of 5-iodo-2'-desoxy-uridine, are obtained.

References

Merck Index 4804
Kleeman and Engel p. 483
DOT 7 (5) 191 (1971) and 10 (10) 268 (1974)
I.N. p. 512
REM p. 1232
Roussel-Uclaf; British Patent 1,024,156; March 30, 1966

**IFENPRODIL TARTRATE**

**Therapeutic Function:** Vasodilator

**Chemical Name:** α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidineethanol tartrate

**Common Name:** -
Structural Formula:

![Chemical Structure Image](image)

Chemical Abstracts Registry No.: 23210-58-4; 23210-56-2 (Base)

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Raw Materials

- Benzyl chloride
- 4-Benzyloxypropiophene
- Hydrogen
- 4-Hydroxypropiophenone
- Bromine
- Tartaric acid

Manufacturing Process

The initial steps involve reacting benzyl chloride with 4-hydroxypropiophenone. The benzyloxypropiophene thus obtained is first brominated and then reacted with 4-benzyloxypropiophenone to give 1-(p-benzyloxyphenyl)-2-(4-benzyl-piperidino)propan-1-one.

The neutral tartrate may be prepared directly by reduction of 1-(p-benzyloxyphenyl)-2-(4-benzyl-piperidino)propan-1-one. For the reduction, a mixture of 175 g of ketone (0.425 mol) and 32 g of tartaric acid (0.213 mol) is hydrogenated at 50°C under pressure of 50 kg/cm² in 440 ml of methanol in the presence of 12 g of palladium on charcoal.

The catalyst is filtered off at elevated temperature, and the filtrate is concentrated by evaporation under reduced pressure to a volume of 300 ml and added in a thin stream to 2.5 liters of diethyl ether with mechanical agitation. The precipitate is separated, washed with diethyl ether and dried in vacuo at 80° to 85°C for several hours. 325 g (96% yield) of the neutral tartrate of 1-(p-hydroxyphenyl)-2-(4-benzyl-piperidino)propan-1-ol are obtained.
IFOSFAMIDE

Therapeutic Function: Antineoplastic

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

Common Name: Isoendoxan

Structural Formula:

Chemical Abstracts Registry No.: 3778-73-2

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<td>Naxamide</td>
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Raw Materials

N-(2-Chloroethyl)amine HCl
N-(2-Chloroethyl)-N,O-propylene phosphoric acid ester amide HCl
Triethylamine

References

Merck Index 4806
Kleeman and Engel p. 484
I.N. p. 513
Manufacturing Process

127.6 g (1.1 mols) of N-(2-chloroethyl)-amine hydrochloride are suspended in a solution of 218 g (1 mol) of N-(2-chloroethyl)-N,O-propylene phosphoric acid ester amide monochloride in 600 cc of methylene dichloride, and 212 g of triethylamine are added thereto dropwise with stirring. The reaction mixture is heated to boiling by the reaction heat. After termination of the addition, the reaction mixture is heated to boiling for another 2 hours. Thereafter, it is cooled to room temperature and the precipitated triethylamine hydrochloride is separated by filtration with suction. The filtrate is extracted with about 60cc of dilute hydrochloric acid (pH 3), then twice with about 60 cc of water, thereafter with about 60 cc of dilute soda lye and finally twice with about 60 cc of water. After drying over anhydrous sodium sulfate, methylene dichloride is distilled off under normal pressure. The oily residue is dried in a vacuum and thereafter extracted in a perforator with 500 cc of anhydrous ether. The oily extract crystallizes upon inoculation and standing in an ice box. After standing for several hours, the precipitate is filtered off, washed with a small amount of cold ether and dried in a vacuum at room temperature. Yield: 185 g (71% of the theoretical). This material is also identified as 3-(2-chloroethyl)-2-(2-chloroethylamino)-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide; generic name: ifosfamide. F.P.: 39°C to 41°C.

References

Merck Index 4807
Kleeman and Engel p. 485
DOT 12 (11) 450 (1976) and 16 (5) 171 (1980)
I.N. p. 513

IMIPENEM

Therapeutic Function: Antibiotic

Chemical Name: 1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-(1-hydroxyethyl)-3-((2-((iminomethyl)amino)ethyl)thio)-7-oxo-, (5R-(5-α,6-α(R*)))-

Common Name: Gorillamicin; Imipemide; Imipenem

Chemical Abstracts Registry No.: 64221-86-9

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<td>Primaxin</td>
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Structural Formula:

Raw Materials

Thienamycin
Methyl formimidate hydrochloride
6-(1)-Hydroxyethyl-1-azabicyclo[3.2.0]heptane-3,7-dione-2-carboxylate
N,S-Bistrimethylsilyl-N-formimidoylcysteamine

Manufacturing Process

Preparation of N-formimidoyl thienamycin:
Thienamycin (517 mg) is dissolved in pH 7 0.1 N phosphate buffer (25 ml) and cooled in an ice bath with magnetic stirring. The solution is adjusted to pH 8.5 using 2.5 N sodium hydroxide solution dispensed from an automatic burette. While maintaining a pH of 8.5, methyl formimidate hydrochloride (711 mg) is added portionwise over 2-3 minutes. After an additional 10 min, the pH of the solution is brought to 7.0 using 2.5 N hydrochloric acid. The solution is chromatographed on a column of XAD-2 resin (150 ml) which is eluted with water. The N-formimidoyl thienamycin derivative (imipenem) elutes in 1.5-2.0 column volumes (200-300 ml) and is lyophilized to a white solid (217 mg). UV (pH 7 0.1 N phosphate buffer); $\lambda_{max}$ 297 nm (8,590); ir (Nujol mull) 1767 Cm$^{-1}$ (β-lactam).

Another method preparation of imipenem:
6-(1)-Hydroxyethyl-1-azabicyclo[3.2.0]heptane-3,7-dione-2-carboxylate is converted to the diphenoxypophosphate enol ester and this in turn reacted with N,S-bistrimethylsilyl-N-formimidoylcysteamine (use of the bistrimethylsilylated reagent is necessary in order to avoid side reactions caused by cyclization reactions). As a result the (PhO)$_2$OPO-groups are converted to Me$_3$SiN = CHNH-groups. Removal of the protecting groups complete the synthesis of 1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-(1-hydroxyethyl)-3-((2-(iminomethyl)amino)ethyl)thio)-7-oxo-, (5R-(5-alpha,6-alpha(R*)))-.

References
Merck Index, Monograph number: 4954, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
IMIPRAMINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 10,11-Dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine hydrochloride

Common Name: Imizin

Structural Formula:

Chemical Abstracts Registry No.: 113-52-0; 50-49-7 (Base)

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Impranil    | Barlow Cote  | Canada   | -                
Impril      | I.C.N.       | -        | -                
Intalpran   | Inter-Alia Pharm. | UK     | -                
Iprogen     | Genethic     | UK       | -                
Iramil      | Knoll        | W. Germany | -              
Melipramin  | EGYT         | Hungary  | -                
Meripramin  | Kanebo, Ltd. | Japan   | -                
Norpramine  | Norton       | UK       | -                
Novopramine | Novopharm    | Canada   | -                
Primonil    | Ikapharm     | Israel   | -                
Prodepress  | Medac        | Australia | -              
Pryleugan   | Arzneimittelwerk Dresden | E. Germany | -            
Psychof orin | Pharmacim    | Bulgaria | -                
Servipramine| Servipharm   | Switz.   | -                
Surplix     | Vis          | Italy    | -                

Raw Materials

- Iminodibenzyl
- 3-Dimethylamino n-propyl chloride
- Sodium amide
- Hydrogen chloride

Manufacturing Process

20 parts of imino dibenzyl are dissolved in 100 parts by volume of absolutely dry benzene. A suspension of 4 parts NaNH₂ in 50 parts by volume of absolute benzene are then added dropwise at 50° to 60°C after which the mixture is boiled for an hour under reflux. 13 parts of 3-dimethylamino n-propyl chloride are then added dropwise at 40° to 50°C and the mixture is boiled for 10 hours under reflux. After cooling, the benzene solution is thoroughly washed with water, whereupon the basic constituents are extracted with dilute hydrochloric acid.

The hydrochloric extract is then made alkaline and the separated base is extracted with ether. After drying, the solvent is evaporated and the residue is distilled in the high vacuum, whereby the N-(3-dimethylaminopropyl)-imino dibenzyl passes over at a temperature of 160°C under 0.1 mm pressure. The chlorohydrate with a melting point of 174° to 175°C is obtained therefrom with alcoholic hydrochloric acid.

References

Merck Index 4817
Kleeman and Engel p. 485
PDR pp. 527, 673, 901, 993, 1569, 1606, 1723
I.N. p. 514
REM p. 1095
Haefliger, F. and Schindler, W.; US Patent 2,554,736; May 29, 1951; assigned to J.R. Geigy AG, Switzerland

**IMPROSULFAN TOSYLATE**

**Therapeutic Function:** Antitumor

**Chemical Name:** Bis-(3-methanesulfonyloxypropyl)amine

**Common Name:** -

**Structural Formula:**

![Structural Formula](image)

**Chemical Abstracts Registry No.:** 13425-98-4 (Base)

**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
--- | --- | --- | ---
Protecton | Yoshitomi | Japan | 1980

**Raw Materials**

- Bis-(3-Methylsulfonyloxypropyl)amine hydrochloride
- Sodium carbonate
- 4-Toluenesulfonic acid

**Manufacturing Process**

A solution of 5 g of bis(3-methylsulfonyloxypropyl)amine hydrochloride in 20 ml of ice water is neutralized with 1N sodium carbonate solution. The resulting amine base is extracted with five 20 ml portions of chloroform. The combined extract is dried over anhydrous sodium sulfate, the solvent is distilled off under reduced pressure, and the residue is dissolved in 20 ml of ethanol. To the ethanol solution is added slowly with stirring under ice cooling a solution of 2.6 g of p-toluenesulfonic acid in 30 ml of ethanol. The white precipitate formed is collected by filtration and recrystallized from ethanol to give 5.0 g of white crystalline bis(3-methylsulfonyloxypropyl)amine p-toluenesulfonate melting at 115°C to 116°C.
INDALPINE

Therapeutic Function: Antidepressant

Chemical Name: 4-[2-(3-Indolyl)ethyl]piperidine

Common Name: -

Structural Formula:

![Structural Formula Image]

Chemical Abstracts Registry No.: 63758-79-2

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Raw Materials

Bis(methoxy-2-ethoxy)sodium aluminum hydride
(Indolyl-3)(piperidinyl-4-methyl)ketone

Manufacturing Process

0.5 g of bis(methoxy-2ethoxy)sodium aluminum hydride in a 70% solution in toluene is added to a solution of 0.29 g of (indolyl-3)(piperidyl-4-methyl) ketone in 10 ml of toluene. The mixture is heated under refluxing conditions for 15 hours, then cooled to 0°C. 10 ml of an aqueous solution of 5N sodium hydroxide is added dropwise thereto, followed by stirring for 1 hour. The organic phase is decanted, washed with water, dried using potassium carbonate and evaporated under partial vacuum. 0.26 g of oil is obtained, which is purified by chromatography and hydrochloride formation. The product
obtained is 0.1 g of (indolyl-3)-2-ethyl-4-piperidine hydrochloride which has a melting point of 167°C.

References

DFU 4 (12) 873 (1979)
DOT 19 (10) 584 (1983)

**INDANAZOLINE**

**Therapeutic Function:** Nasal decongestant

**Chemical Name:** 2-(4-Indanylamino)-2-imidazoline

**Common Name:** -

**Structural Formula:**

![Structural formula](image)

**Chemical Abstracts Registry No.:** 40507-78-6

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**Raw Materials**

- N-4-Indanyl thiourea
- Methyl iodide
- Ethylene diamine

**Manufacturing Process**

38.5 g (0.1 mol) of N-4-indanyl thiourea are dissolved in 250 cc of methanol. 42.6 g (0.3 mol) of methyl iodide are added thereto and the mixture is refluxed for 2.5 hours. The mixture thereafter is cooled and the solvent is removed in a rotation evaporator in a vacuum. Thus, 57.5 g of N-4-indanyl-S-methylisothiuronium hydroiodide (86% of theoretical) are obtained. Melting point 144°C to 146°C.
33.49 (0.1 mol) of N-4-indanyl-S-methylisothiuronium hydroiodide are mixed with 9.0 g (0.15 mol) of anhydrous ethylenediamine. The mixture is slowly heated to 80°C and heating is continued until the termination of the formation of methylmercaptan (about 4 hours). After cooling the residue is dissolved in 2N hydrochloric acid and the solution is extracted with chloroform. The extract is discarded and the aqueous phase is rendered alkaline by the addition of 10% soda lye. The resulting solution is extracted with chloroform and the extract is washed with water, dried over anhydrous sodium sulfate and the solvent is removed. An oily residue is obtained which upon standing soon crystallizes.

The product is recrystallized from petroleum ether having a boiling range of 100°C to 140°C in the presence of activated carbon. Thus, 11.1 g of 2-(4-indanylamino)-2-imidazoline (55% of theoretical) are obtained as the free base. Melting point 109°C to 113°C.

References

Merck Index 4826
DFU 6 (7) 417 (1981)
DOT 17 (10) 413 (1981)
I.N. p. 516
May, H.J. and Berg, A.; US Patent 3,882,229; May 6, 1975; assigned to Nordmark-Werke GmbH

INDANOREX

Therapeutic Function: Anorexic

Chemical Name: 1H-Inden-2-ol, 2-(1-aminopropyl)-2,3-dihydro-

Common Name: Indanorex

Structural Formula:

![Structural Formula](image)

Chemical Abstracts Registry No.: 16112-96-2

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Raw Materials

- Pyridine
- 2-Cyano-2-hydroxyindane
- Ethyl bromide
- Trimethylchlorosilane
- Magnesium
- Sodium borohydride

Manufacturing Process

125 g (1.15 mol) trimethylchlorosilane was added to 159 g (1 mol) 2-cyano-2-hydroxyindane in 600 ml pyridine by stirring for 2 hours, whereupon the mixture was heated at 1 hour at 40°C for 1 hour. A light precipitate was filtered off and washed with 1 liter of benzene. The filtrate was washed with water, dried over magnesium sulfate and concentrated in vacuum. The residue was dissolved in benzene 2 times and 2 times the solvent was removed in vacuum in order to any pyridine and water was present. Yield of silano-organic compound as a clear brown liquid was 230 g (100%); BP: 95°C/15 mm Hg.

10.5 g magnesium in 30 ml of dry ether was mixed with 55.5 g of ethyl bromide in 62 ml ether during about 1 hour at the temperature of boiling ether. After that the mixture was heated to 45°C in order to finish the synthesis of ethyl magnesium bromide. On cooling to 0°C it was stood for 2 hours and 50 g the above prepared silano-organic compound in 620 ml ether was added at the temperature about 5°C, whereupon in was stirred else 30 minutes at the ambient temperature and then was placed into ice bath. 82 ml of methanol was added to the prepared mixture during 1 hour. The temperature was kept about 18°C. On 30 minutes stirring the mixture was evaporated to 1/3 volume in vacuum at the temperature about 20°C. The residue was with ethanol diluted, the ethanol was evaporated, whereupon 100 ml methanol was added. 16.4 g sodium borohydride was added to the methanol solution for 1 hour at ice cooling, and stirred 2 hours at 3°C. It stood at ambient temperature overnight. Then the mixture was cooled to 10°C. 250 ml of hydrochloric acid (conc.) was added. After that it was heated at 45°C for 1 hour. The solvent was removed to dryness in vacuum. The pasty residue was in 250 ml of water dissolved and with chloroform washed. The 2-(1-aminopropyl)-2-indanol was precipitated by adding of 750 ml 10% sodium carbonate to pH 10. It was extracted with chloroform and dried over magnesium sulfate.

Chloroform was evaporated to give 13 g desired 2-(1-aminopropyl)-2-indanol. MP: 92°C. Yield 33%. IR spectrum and thin layer chromatography confirmed the structure of prepared compound.

References


INDAPAMIDE

Therapeutic Function: Diuretic
Chemical Name: 3-(Aminosulfonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl)-benzamide

Common Name: Metindamidem

Structural Formula:

![Chemical Structure](image)

Chemical Abstracts Registry No.: 26807-65-8

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Raw Materials

3-Sulfamyl-4-chloro-benzoyl chloride
N-Amino-2-methyl indoline

Manufacturing Process

A total of 8.9 parts of 3-sulfamyl-4-chloro-benzoyl chloride in a solution of 50 parts of anhydrous tetrahydrofuran are added portionwise in the course of 60 minutes, while stirring, to a solution of 5.2 parts of N-amino-2-methyl indoline and 3.5 parts of triethylamine in 150 parts of anhydrous tetrahydrofuran. The reaction mixture is left to stand 3 hours at room temperature, then the precipitated chlorhydrate of triethylamine is filtered off. The filtrate is evaporated under vacuum and the residue is crystallized from a solution of 60 parts of isopropanol in 75 parts of water. There are obtained 9 parts of N-(3-sulfamyl-4-chlorobenzamido)-2-methyl indoline, MP (K) 184° to 186°C, MP (MK) 160° to 162°C (isopropanol/water). [The melting points being
determined on a Kofler heater plate under the microscope (MK) or on a Kofler Bank (K).

References

Merck Index 4828
Kleeman and Engel p. 487
PDR p. 1816
DOT 12 (8) 313 (1976) and 13 (1) 41 (1977)
I.N. p. 516
REM p. 944
Beregl, L., Hugon, P., Laubie, M.; US Patent 3,56591 1; February 23,1971; assigned to Science Union et Cie, Societe Francaise de Recherche Medicale, France

INDENOLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1-[1H-Inden-4(or 7)-yloxy]-3-[(1-methylethyl)amino]-2-propanol

Common Name: -

Structural Formula:

![Structural Formula](image)

Chemical Abstracts Registry No.: 60607-68-3

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Raw Materials

4-Hydroxyindene
Isopropylamine
Epichlorohydrin
Hydrogen chloride
**Manufacturing Process**

(a) A mixture of 0.9 g of 4-hydroxyindene, 2.0 g of 1,2-epoxy-3-chloropropane (epichlorohydrin), 2.7 g of potassium carbonate and 15 ml of acetone was refluxed at about 57°C for 24 hours. Acetone was removed by vacuum distillation, the residue was washed with 10 ml of water and then extracted with 20 ml of ether three times. The ether extract was dried with magnesium sulfate, filtered and subjected to column chromatography using a column (having an inside diameter of about 3 cm and a height of about 50 cm) packed with silica gel. The 5th to 7th fractions (volume of one fraction is 50 ml) recovered from the chromatographic column using chloroform as the effluent were combined together and concentrated to provide 0.6 g of 4-(2,3-epoxypropoxy)indene.

(6) A mixture of 0.42 g of 4-(2,3-epoxypropoxy)indene, 1.20 g of isopropylamine and 20 ml of methanol was stirred in a flask at room temperature for 2 hours. Methanol and unchanged isopropylamine were removed by vacuum distillation and the residue was recrystallized from a mixture of n-hexane and ether to yield 0.41 g of 4-(3-isopropylamino-2-hydroxypropoxy)indene having a melting point of 88°C to 89°C.

(c) To a solution of 0.41 g of 4-(3-isopropylamino-2-hydroxypropoxy)indene in 80 ml of absolute ether there was added dropwise a hydrochloric acid-ether mixture at 0°C with stirring. The precipitates thus formed were recovered by filtration and recrystallized from a mixture of ethanol and ether to provide 0.44 g of the hydrochloride of 4-(3-isopropylamino-2-hydroxypropoxy)indene. Melting point 147°C to 148°C.

**References**

Merck Index 4831  
DFU 2 (11) 730 (1977)  
Kleeman and Engel p. 487  
DOT 16 (1) 24 (1980)  
I.N. p. 516  

**INDOMETHACIN**

**Therapeutic Function:** Antiinflammatory

**Chemical Name:** 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

**Common Name:** -
### Structural Formula:

![Structural Formula](image)

### Chemical Abstracts Registry No.: 53-86-1

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1902 Indomethacin

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**Raw Materials**

- t-Butyl alcohol
- Sodium hydride
- p-Chlorobenzoyl chloride

**Manufacturing Process**

(A) 2-Methyl-5-Methoxy-3-Indolylacetic Anhydride: Dicyclohexylcarbodiimide (10 g, 0.049 mol) is dissolved in a solution of 2-methyl-5-methoxy-3-
indolylacetic acid (22 g, 0.10 mol) in 200 ml of THF, and the solution is allowed to stand at room temperature for 2 hours. The precipitated urea is removed by filtration, and the filtrate is evaporated in vacuo to a residue and flushed with Skellysolve 6. The residual oily anhydride is used without purification in the next step.

(B) t-Butyl 2-Methyl-5-Merhoxy-3-Indolylacetate: t-Butyl alcohol (25 ml) and fused zinc chloride (0.3 g) are added to the anhydride from Part A. The solution is refluxed for 16 hours and excess alcohol is removed in vacuo. The residue is dissolved in ether, washed several times with saturated bicarbonate, water, and saturated salt solution. After drying over magnesium sulfate, the solution is treated with charcoal, evaporated, and flushed several times with Skellysolve B for complete removal of alcohol. The residual oily ester (18 g, 93%) is used without purification.

(C) t-Buryl 1-p-Chlorobenzoyl-2-Methyl-5-Mefhoxy-3-Indolylacetate: A stirred solution of ester (18 g, 0.065 mol) in dry DMF (450 ml) is cooled to 4°C in an ice bath, and sodium hydride (4.9 g, 0.098 mol, 50% susp.) is added in portions. After 15 minutes, p-chlorobenzoyl chloride (15 g, 0.085 mol) is added dropwise during 10 minutes, and the mixture is stirred for 9 hours without replenishing the ice bath. The mixture is then poured into one liter of 5% acetic acid, extracted with a mixture of ether and benzene, washed thoroughly with water, bicarbonate, saturated salt, dried over magnesium sulfate, treated with charcoal, and evaporated to a residue which partly crystallizes. This is shaken with ether, filtered and the filtrate is evaporated to a residue (17 g) which solidifies after being refrigerated overnight.

The crude product is boiled with 300 ml of Skellysolve 6, cooled to room temperature, decanted from some gummy material, treated with charcoal, concentrated to 100 ml, and allowed to crystallize. The product thus obtained (10 g) is recrystallized from 50 ml of methanol and gives 4.5 g of analytically pure material, MP 103° to 104°C.

(D) 1 -p-Chlorobenzoyl-2-Methyl-5-Methoxy-3-Indolylacetic Acid: A mixture of 1 g ester and 0.1 g powdered porous plate is heated in an oil bath at 210°C with magnetic stirring under a blanket of nitrogen for about 2 hours. No intensification of color (pale yellow) occurs during this period. After cooling under nitrogen, the product is dissolved in benzene and ether, filtered, and extracted with bicarbonate. The aqueous solution is filtered with suction to remove ether, neutralized with acetic acid, and then acidified weakly with dilute hydrochloric acid. The crude product (0.4 g, 47%) is recrystallized from aqueous ethanol and dried in vacuo at 65°C: MP 151°C.

References

Merck Index 4852
Kleeman and Engel p. 488
PDR pp.993, 1034, 1187, 1354, 1606, 1999
DOT 1 (4) 125 (1965); 18 (8) 373 (1982) and 19 (5) 286 (1983)
I.N. p. 517
REM p. 1118
INDOPROFEN

Therapeutic Function: Antiinflammatory

Chemical Name: 4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-α-
methylbenzeneacetic acid

Common Name: -

Structural Formula:

![Structural formula of indoprofen]

Chemical Abstracts Registry No.: 31842-01-0

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Raw Materials

- Ethyl-α-(4-aminophenyl)propionate
- Ethyl 2-chloromethyl benzoate
- Potassium hydroxide

Manufacturing Process

The mixture of 7.9 g of ethyl α-(4-aminophenyl)propionate and 8.3 g of ethyl 2-chloromethyl benzoate is refluxed under nitrogen for one hour. The residue is recrystallized from hexane, to yield the ethyl α-[4-(1-oxo-isoindolino)-phenyl]-propionate of the formula melting at 104° to 106°C. The mixture of 4.5 g thereof, 1.6 g of potassium...
hydroxide, 2 ml of water and 250 ml of ethanol is refluxed under nitrogen for 2 hours and evaporated under reduced pressure. The residue is taken up in water, the solution washed with chloroform, acidified with hydrochloric acid and extracted with ethyl acetate. The extract is dried, evaporated and the residue recrystallized from ethyl acetate, to yield the corresponding free acid melting at 208° to 210°C. (Procedure reported in US Patent 3,767,805.)

References

Merck Index 4853
DFU 1 (5) 242 (1976)
Kleeman and Engel p. 489
DOT 13 (5) 200 (1977)
I.N. p. 517
Carney, R.W.J. and de Stevens, G.; US Patent 3,767,805; October 23, 1973; assigned to Ciba-Geigy Corporation
Carlo Erba, S.P.A., Italy; British Patent 1,344,663; January 23, 1974

INDORAMIN

Therapeutic Function: Antihypertensive

Chemical Name: N-[1-[2-(1H-Indol-3-yl)ethyl]-4-piperidinyl]benzamide

Common Name: -

Structural Formula:

Chemical Abstracts Registry No.: 26844-12-2

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Raw Materials

4-Benzamido-1-(2-(3-indolyl)ethyl]pyridinium bromide
Hydrogen
Manufacturing Process

4-Benzamido-1-[(2-(3-indoyl)ethyl] pyridinium bromide (3.0 g) was dissolved in 91% ethanol (300 ml) containing triethylamine (0.08 g) and freshly prepared W7 Raney nickel catalyst (ca 3 g) was added. The mixture was hydrogenated in an autoclave at 400 psi hydrogen pressure and 50°C for 4 hours. After filtering off the catalyst the filtrate was evaporated in vacuo and the residue was shaken with a mixture of chloroform and 2N sodium hydroxide solution. The resulting insoluble material was filtered off and dried to give 1.61 g of product, MP 203°C to 206°C. Recrystallization from ethanol gave the title compound as colorless needles (1.34 g), MP 208°C to 210°C.

References

Merck Index 4854
DFU 1 (10) 476 (1976)
OCDS Vol. 2 p. 344 (1980)
DOT 17 (10) 420 (1981)
I.N. p. 518
Archibald, J.L. and Jackson, J.L.; US Patent 3,527,761; September 8, 1970; assigned to John Wyeth and Brother, Ltd. (UK)

INOSINE

Therapeutic Function: Cardiotonic

Chemical Name: 9-β-D-Ribofuranosylhypoxanthine

Common Name: Hypoxanthine riboside

Structural Formula:

Chemical Abstracts Registry No.: 58-63-6

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Trophicardyl | Innothera | France | -
Virusina | Dukron | Italy | -

**Raw Materials**

- Adenosine
- Barium nitrite
- Sulfuric acid

**Manufacturing Process**

As described in US Patent 3,049,536, inosine may be prepared starting with adenosine.

The Deamination of Adenosine: 20 g of adenosine are dissolved in one liter of water by warming, and after cooling to room temperature 120 g of barium nitrite (monohydrate) are added to the solution. Under stirring there is added in time intervals of one hour 160 cc of 2 N sulfuric acid after each time interval. After the third addition, the reaction mass is allowed to stand for 3 hours at room temperature. The solution is then tested for barium, and if some barium is still present a slight excess of sulfuric acid is added. 300 cc of methanol is then added. In order to drive off the excess of nitrous acid, CO₂ is conducted through the solution until the solution is free of nitrous acid as determined by testing with potassium iodide-starch paper. The precipitated barium sulfate is separated by centrifugation. The residue is washed one time with about 500 cc of water. The total volume of the centrifugate is about 2.3 liters.

Isolation of Inosine by Ion Exchange Method: Half of the above clear centrifugate (1.15 liters) is treated with 250 cc of anion exchange (bicarbonate form) and stirred together therewith for 16 hours at room temperature. The pH value is increased thereby to about 4 to 5. The ion exchanger is filtered off under suction and washed 3 times, each time with 150 cc of water. The solution is brought to a pH value of 7 by means of normal sodium hydroxide (total volume of the solution about 1.55 liters), and concentrated to a volume of about 100 cc under vacuum.

The inosine is crystallized overnight in an ice box and the inosine is then filtered off by suction, washed with a small amount of ice water and dried at a temperature of 105°C. A first fraction of crude inosine consisting of 5.4 g having a purity of 99% is obtained. Further fractions of crude inosine are obtained from the mother liquid by concentration, the total amount constituting 3.2 g having a purity of 96 to 98%. The yield of crude inosine is 8.6 g which is equal to 86%.

Recrystallization of the Crude Inosine: 17.0 g of crude inosine are dissolved in 400 cc of 80% ethanol in a water bath, filtered while hot and brought to crystallization in an ice box. After standing overnight the crystalline material is filtered off under suction and washed with ice water. The pure inosine is dried in a drying chamber at a temperature of 105°C. The yield of pure inosine is 15.0 g which is equal to 75%. The yield can be further increased by working
up the mother liquor of the crystallization as set forth above.

Alternatively, inosine may be made by fermentation as described in US Patent 3,111,459. 3 ml portions of a culture medium consisting of glucose (5 g/dl), ammonium chloride (0.4 g/dl), urea (0.4 g/dl), KH₂PO₄ (0.1 g/dl), MgSO₄ · 7H₂O (0.02 g/dl), Mn⁺⁺ (2 ppm), Fe⁺⁺ (2ppm), casein hydrolyzate (0.2 g/dl), yeast extract (0.2 g/dl), corn steep liquor (0.2 ml/dl), polypeptone (0.1 g/dl), meat extract (0.1 g/dl) and sodium ribonucleate (10 mg/dl) were poured into respective test tubes and each tube was sterilized at 115°C for 10 minutes. Thereafter separately sterilized calcium carbonate was added in the amount of 2 g/dl and then cells of Bacillus subtilis S26910 were inoculated into the above media and cultured with shaking at 30°C for 20 hours.

The resulting culture liquids were utilized for seeding, 20 ml of the medium having the composition described above were poured into a 500 ml shaking flask and sterilized at 115°C for 10 minutes and five drops of the above seed were added, and then cultured with shaking at 30°C for 65 hours. Thereafter 0.15 g/dl of inosine were accumulated.

The inosine-containing solution, which was obtained by separating the cells from the resulting fermentation liquid, was treated with both decolorizing resins and anion exchange resins by means of a conventional method and then acetone was added to crystallize the inosine. 1.47 g of the crude crystals of inosine were obtained from 3.5 liters of the culture liquid containing 1 g of inosine per liter.

References

Merck Index 4858
I.N. p. 519
Reiff, F., Huber, G. and Holle, K.; US Patent 3,049,536; August 14, 1962; assigned to Zellstoff Fabrik Waldhof, Germany

INOSITOL

Therapeutic Function: Vitamin, Lipotropic

Chemical Name: Myo-Inositol

Common Name: Hexahydroxycyclohexane; Cyclohexitol

Chemical Abstracts Registry No.: 87-89-8

Raw Materials

Starch
Calcium hydroxide
Inactive inositol may be prepared from starch factory steep water which is the liquid in which corn is steeped to soften the covering of the corn kernel and to thoroughly soften the entire kernel. It contains approximately 1% sulfurous acid (H$_2$SO$_3$) in solution. A typical example of such treatment consists in adding to the acid steep water, lime Ca(OH)$_2$ or CaO to approximate neutrality, or to a pH of 6.0 to 8.0, at which range the insoluble "phytin" is precipitated. This precipitate of impure "phytin" or calcium phytate is removed by suitable means, as stated before, and may be mixed with (1) 1 to 10% acid solution; or (2) diluted with water; or (3) the solution may be made alkaline. This alkaline or neutral or acid mixture is placed in a suitable container in an autoclave or steam digester, and the steam turned on whereupon the reaction is allowed to proceed as long as desired. The autoclave in which the mixture has been placed may be heated by generating steam therein, by means of an electric heater, or by suitable heat from outside. A pressure of from 1 to 200 pounds steam for 1 to 18 hours may be used, the time required being correspondingly less for higher pressures. A suitable pressure is 80 pounds. The time expected for 80 pounds is three hours.

After hydrolysis or decomposition is complete, pressure is released, the autoclave cooled, the mixture removed, diluted, and made alkaline with Ca(OH)$_2$, Ba(OH)$_2$, etc., brought to boiling, thoroughly agitated with steam, the insoluble sludge allowed to settle, and the supernatant liquid removed by decantation, siphoning or filtration. The supernatant liquid is concentrated in an open vessel, or in vacuum, to remove the precipitating inorganic impurities as calcium carbonate (CaCO$_3$), magnesium carbonate (MgCO$_3$), etc. The liquid is concentrated until it becomes thick and syrupy. The concentrated solution is filtered, cooled, and agitated by a suitable mechanical means to precipitate L-inositol. The D-inositol is removed by filtration, the mother liquor concentrated, and the process repeated until the solution becomes too thick to filter advantageously. A filter press may be employed to remove further
quantities of i-inositol, or the thick residue may be diluted with a reagent in which i-inositol is insoluble; as, for example, acetic acid (CH\textsubscript{3}COOH) and alcohol-acetic acid (C\textsubscript{2}H\textsubscript{5}OH, CH\textsubscript{3}COOH, etc.). On cooling and stirring the solution, additional i-inositol, etc., results and can be removed by filtration or other mechanical means. The i-inositol may be recrystallized by dissolving the crude product in boiling water, and reprecipitated by cooling and stirring. The final crystallization from a hot water solution to which an equal volume of alcohol is added with cooling and stirring, gives a purer product.

References

Merck Index 4861
PDR pp. 581, 1033, 1263, 1734
I.N. p. 519
REM p. 1015
assigned to American Cyanamid Co.

INOSITOL NIACINATE

Therapeutic Function: Vasodilator

Chemical Name: Myo-Inositol hexa-3-pyridine carboxylate

Common Name: Inositol hexanicotinate

Structural Formula:

Chemical Abstracts Registry No.: 6556-11-2
**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
--- | --- | --- | ---
Hexanicotol | Philadelphia | US | 1962
Dilexpal | Winthrop | France | 1968
Bendigon | Bayer | W. Germany | -
Clevamin | Kowa | Japan | -
Cycnate | Toyo | Japan | -
Ebelin | Samva | Japan | -
Hammovenad | Bastian Werk | W. Germany | -
Hexalmin | Maruishi | Japan | -
Hexainosineat | Hishiyama | Japan | -
Hexanate | Nippon Chemiphar | Japan | -
Hexanicit | Yoshitomi | Japan | -
Hexate | Mohan | Japan | -
Hexatin | Kobayashi | Japan | -
Hexit | Toho | Japan | -
Inochinate | Nichiiko | Japan | -
Inosinit | Kanto | Japan | -
Kotanicit | Kotani | Japan | -
Mesonex | Tokyo Tanabe | Japan | -
Mesosit | Toyo Jozo | Japan | -
Nasky | Nikken | Japan | -
Neonitin | Chugai | Japan | -
Nicosamin | Toyama | Japan | -
Nicosinate | Toyo Ono | Japan | -
Nicosinit | Hokuriku | Japan | -
Nicotol | Maruko | Japan | -
Nicoxatin | Fuso | Japan | -
Romanit | Kowa | Japan | -
Salex | Iwaki | Japan | -
Sanneicit | Sanko | Japan | -
Secotinen | Seiko | Japan | -
Shikioit | Shiri | Japan | -
Xatolone | Showa | Japan | -
Yonomol | Sawai | Japan | -

**Raw Materials**

Nicotinic acid
Phosphorus oxychloride
meso-Inositol

** Manufacturing Process**

100 g of nicotinic acid were suspended in 265 ml of distilled and dried pyridine without stirring. 68 g of phosphorus oxychloride were added dropwise to this mixture under continual stirring. The temperature of the reactants, initially at 20°C, was allowed to rise to about 60°C, and this temperature was maintained for a further 60 minutes. Thereafter 24.5 g of meso-inositol were
added gradually, the temperature being controlled so that it did not exceed about 80°C. The reactants were maintained at this temperature for from 2 to 3 hours, and thereafter the reaction mixture was poured into 500 ml of water. The pyridine salts formed during the reaction readily dissolved, and the meso-inositol hexanicotinate which had formed crystallized out. The ester was filtered off and washed with water and acetone or alcohol. Finally, the meso-
inositol hexanicotinate was dried at 100°C.

The yield was 90%, the melting point of the product was 258°C to 260°C. and the chlorine content <0.01%.

References

Merck Index 4863
Kleeman and Engel p. 490
I.N. p. 519
A.B. Bofors; British Patent 1,053,689; January 4, 1967

INSULIN

Therapeutic Function: Antidiabetic

Chemical Name: Complex polypeptide hormone with molecular weight over 6,000

Common Name: -

Structural Formula: A protein that has the normal structure of the natural antidiabetic principle produced by the human pancreas

Chemical Abstracts Registry No.: 9004-10-8

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<td>Lilly</td>
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Raw Materials

Beef pancreas glands
Ethanol

Manufacturing Process

40 pounds of frozen beef pancreas glands were hashed and extracted by stirring with 45,500 cc of 85% alcohol containing 925 cc of phosphoric acid. The acidity of the extraction mixture was pH 3.0 and the alcohol concentration approximately 65% after equilibrium was attained. The pancreatic meat solids removed were then reextracted by stirring in 45,000 cc of 65% alcohol. The pH of the combined filtrates was raised to pH 8.0 by addition of ammonium hydroxide to precipitate inert proteins and phosphoric acid salts. The solids were removed by filtration and sulfuric acid was then added to the filtrate to bring the pH to 3.5. The acidified extracts were then concentrated under reduced pressure to an alcohol concentration of 20%. Lipoidal material was removed by filtration and the filtrate concentrated under reduced pressure to the aqueous phase. Lipoidal material was then removed by filtration and the insulin containing filtrate biologically assayed for insulin activity. The biological assay showed the insulin recovered to be equivalent to 1425 I.U. for each pound of pancreas glands processed.

References

Merck Index 4866
PDR pp. 1054, 1270, 1777
DOT 19 (2) 111 and (5) 262 (1983)
REM p. 973

INSULIN ISOPHANE

Therapeutic Function: Hypoglycemic

Chemical Name: See structure

Common Name: Isophane insulin injection

Structural Formula: Isophane insulin

Chemical Abstracts Registry No.: 53027-39-7

<table>
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<td>NPH-Iletin</td>
<td>Lilly</td>
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<td>Novo</td>
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<td>Humulin-I</td>
<td>Lilly</td>
<td>UK</td>
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Raw Materials

- Zinc insulin
- Selmiridine sulfate

Manufacturing Process

This is a crystalline product of insulin and an alkaline protein where the protein/insulin ratio is called the isophane ratio. This product gives a delayed and uniform insulin action with a reduction in the number of insulin doses necessary per day. Such a preparation may be made as follows: 1.6 g of zinc-insulin crystals containing 0.4% of zinc are dissolved in 400 ml of water, with the aid of 25 ml of 0.1 N hydrochloric acid. To this are added aqueous solutions of 3 ml of tricresol, 7.6 g of sodium chloride, and sufficient sodium phosphate buffer that the final concentration is 1/75 molar and the pH is 6.9. Then 0.14 g of salmiridine sulfate dissolved in water is added, while shaking. Salmiridine is a protamine derived from the sperm of Salmo irideus Gibbons, or rainbow trout. Salmiridine-insulin (a protamine-insulin) containing zinc is promptly precipitated. Enough water is now added to make a total of one liter, and the whole is shaken again. After standing for about an hour, the precipitated salmiridine-insulin is found to have become crystalline.

This crystalline salmiridine-insulin can be removed if desired, as by filtration; but it is not necessary to do that, as the suspension of crystalline salmiridine-insulin may be preserved as thus prepared, and dispensed and used (in the same manner as known preparations of protamine insulin and protamine-zinc-insulin are used) in the original suspending medium in which it is formed.

References

PDR p.1778
REM p.974

INSULIN ZINC SUSPENSION

Therapeutic Function: Hypoglycemic

Chemical Name: Insulin zinc suspension

Common Name: -
**Structural Formula:** Sterile suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride in a manner such that the solid phase of the suspension consists of a mixture of crystals and amorphous material in a ratio of approximately 7:3

**Chemical Abstracts Registry No.:** 8049-62-5

<table>
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<td>Lente Insulin</td>
<td>Squibb</td>
<td>US</td>
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<td>Lilly</td>
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<td>Protamine</td>
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<td>Semilente</td>
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<td>Ultralente</td>
<td>Squibb-Novo</td>
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**Raw Materials**

- Insulin
- Zinc chloride

**Manufacturing Process**

First, a series of stock solutions are made.

Stock Solution 1: 2.18 g of recrystallized insulin are dissolved in 25 ml of 0.1 N hydrochloric acid, and distilled water to a volume of 125 ml is added.

Stock Solution 2: To 20 ml of an aqueous zinc chloride solution containing 1% zinc is added distilled water to a volume of 125 ml.

Stock Solution 3: 1.36 g of sodium acetate with 3 mols crystal water are dissolved in distilled water to a volume of 100 ml.

Then, 1.3 ml of glycerine are mixed with 0.5 ml of a 25% solution of methyl p-hydroxybenzoate in ethanol, and 50 ml of distilled water are added. To the produced mixture are, after sterile filtration, added 10 ml of the stock solution 1, 2.5 ml of the stock solution 2 and 10 ml of the stock solution 3, after which 3.0 ml of sterile 0.1 N sodium hydroxide are added, and the mixture is filled up with sterile distilled water to a volume of 100 ml. The insulin will be precipitated amorphously by the admixture of the sodium hydroxide, and the produced suspension acquires the pH value of 7. It will contain approximately 1 gamma zinc per insulin unit.

**References**

Merck Index 4869
PDR pp. 1055, 1777
REM p.975
Petersen, K., Schlichtkrull, J. and Halias-Moller, K.; US Patent 2,882,203; April 14, 1959 assigned to Novo Terapeutisk Laboratorium A/S, Denmark

**Trade Name**

- **Lente Insulin**
  - **Manufacturer:** Squibb
  - **Country:** US
  - **Year Introduced:** 1971

- **Iletin I**
  - **Manufacturer:** Lilly
  - **Country:** US
  - **Year Introduced:** -

- **Protamine**
  - **Manufacturer:** Lilly
  - **Country:** US
  - **Year Introduced:** -

- **Semilente**
  - **Manufacturer:** Squibb-Novo
  - **Country:** US
  - **Year Introduced:** -

- **Ultralente**
  - **Manufacturer:** Squibb-Novo
  - **Country:** US
  - **Year Introduced:** -
INTERFERON

Therapeutic Function: Antineoplastic, Antiviral

Chemical Name: See structural Formula

Common Name: -

Structural Formula: Interferons (complex protein)

Chemical Abstracts Registry No.: 9008-11-1

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<td>Fiblaferon</td>
<td>Bioferon</td>
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<td>Wellferon</td>
<td>Burroughs-Wellcome</td>
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Raw Materials

- Semliki Forest arborvirus
- Animal kidneys
- Trypsin

Manufacturing Process

Semliki Forest arborvirus was grown in chick embryo tissue culture. The infectious tissue culture liquid was decanted and diluted with medium 199 to give a preparation containing between $10^6$ and $10^6.5$ mouse ID$_{50}$ of virus/ml.

Calf kidneys, dog kidneys and rhesus monkey kidneys were treated with trypsin to give suspensions of cells. The suspensions were centrifuged and the packed cells diluted with 400 volumes (calf cells) or 200 volumes (dog cells and rhesus monkey cells) of a growth medium consisting of 5% horse serum and 0.5% lactalbumen hydrolysate in Earle's saline, with 100 units/ml each of penicillin and streptomycin. These media were used separately to produce Semliki Forest/calf interferon, Semliki Forest/dog interferon and Semliki Forest/rhesus monkey interferon. The cell-containing growth medium was dispensed into 500 ml medical flat bottles (70 ml in each). The cultures were incubated at 36°C. Confluent sheets of cells (monolayers) were formed in 5 to 6 days. The growth medium was then removed and the monolayers were washed with isotonic phosphate-buffered saline, pH 7.5.

Each bottle for interferon production received the arborvirus preparation in medium 199 (0.5 ml) and further medium 199 (50 ml); some bottles received only medium 199 (50 ml) and no virus and served as controls. The bottles were incubated for 3 to 5 days at 36°C.

The supernatants containing the interferons were decanted from monolayers, pooled, and tested for freedom from bacteria. Residual arborvirus was inactivated by acid and heat as follows. The liquid was brought to pH 2 by the addition of 0.3N hydrochloric acid in Earle's saline (minus sodium chloride and sodium bicarbonate), kept at 4°C for 24 hours, and then brought back to pH 7.
by the addition of 0.3N sodium hydroxide in distilled water. The liquid was then heated at 56°C for 30 minutes.

At this stage the interferon preparations were assayed and submitted to safety tests for the absence of contaminating viruses.

Rhesus monkey kidney infected with Semliki Forest arborvirus gave interferon of titre 1.5 log interferon units/2 ml. (The interferon unit, determined in a volume of 2 ml, is the dilution of interferon which produced a half-maximal score for degree of cytopathic effect in virus-infected tissue culture tubes at the time when the control without interferon first showed the maximal score.)

Each interferon preparation was ultracentrifuged at 20,000 revolutions per minute for one hour to remove tissue debris and inactivated virus. The supernatant was dialyzed against distilled water (1:400) for 24 hours at 4°C. The material was then freeze-dried. The dried product was reconstituted in one-tenth of the original volume in distilled water and dispensed into ampoules. Reconstituted solutions were assayed for interferon activity, examined for toxicity, and tested for sterility.

References

Merck Index 4870
DOT 18 (8) 393 (1982)
I.N. p. 520
REM p. 1233
Sellers,R.F.; British Patent 960,769; June 17, 1964; assigned to The Wellcome Foundation Ltd. (UK)

**IOBENZAMIC ACID**

**Therapeutic Function:** Diagnostic aid

**Chemical Name:** β-Alanine, N-(3-amino-2,4,6-triiodobenzoyl)-N-phenyl-

**Common Name:** Acide iobenzamique; Acidum iobenzamicum; Acidum jobenzamicum; Iobenzamic acid

**Structural Formula:**
Chemical Abstracts Registry No.: 3115-05-7

**Trade Name | Manufacturer | Country | Year Introduced**
--- | --- | --- | ---
Bilibyk | Byk Gulden | - | -
Osbil | Upjohn | - | -
Osbil | M and B | - | -

**Raw Materials**

- Methyl β-anilinopropionate
- 3-Amino-2,4,6-triiodobenzoyl chloride
- Hydrogen chloride
- Sodium hydroxide

**Manufacturing Process**

1013.2 g 3-amino-2,4,6-triiodobenzoyl chloride are dissolved in a minimum amount of hot dioxane and caused to flow into 700.6 g molten methyl β-anilinopropionate with stirring. After the ensuing exothermic reaction has gradually terminated the reaction mixture is heated on a steam bath for about 3 h and while boiling hot has then methanol and methanolic 3 N HCl added thereto, where after it is cooled. The precipitated solids are separated and washed with ether. 953.0 g methyl β-N-(3-amino-2,4,6-triiodobenzoyl)-phenylaminopropionate are obtained having a melting point of 156°-157°C. Yield 74.2% of theory.

The methyl ester may be precipitated as the free acid by dissolving in dioxane, addition of 3.15 N methanolic sodium hydroxide solution, pouring the resulting reaction mixture in water, and acidulating the solution with 6 N HCl. After separation and drying, 553.6 g β-N-(3-amino-2,4,6-triiodobenzoyl)-phenylaminopropionic acid having a melting point of 133°-134.5°C are obtained from 571.0 g methyl ester. Overall yield 73.46% of theory.

**References**


**IOCARMIC ACID**

**Therapeutic Function:** Diagnostic aid

**Chemical Name:** Benzoic acid, 3,3′-((1,6-dioxo-1,6-hexanediyl)diimino)bis(2,4,6-triiodo-5-((methylamino)carbonyl))- 

**Common Name:** Acide iocarmique, Acidum iocarmicum, Acidum iocarmicum, Iocarmate meglumine, Iocarmic acid, Meglumine iocarmate
**Structural Formula:**

![Structural Formula Image]

**Chemical Abstracts Registry No.:** 10397-75-8

**Raw Materials**

- Acetic acid
- Adipoyl chloride
- Hydrochloric acid
- 5-Amino-2,4,6-triiodo-N-methylisophthalamic acid
- Dimethylacetamide
- Sodium hydroxide

**Manufacturing Process**

5-Amino-2,4,6-triiodo-N-methylisophthalamic acid (228.0 g, 4 mole) was added to stirred, heated dimethylacetamide (400 ml). When the temperature reached 95°C, adipoyl chloride (27.5 g, 0.15 mole) was added all at once, followed by an equal amount added slowly over a period of 15 min (a total of 55.0 g). After addition of the adipoyl chloride the solution was stirred at about 95°C for another 15 min, then poured into 2 L of hot water. As the above mixture cooled to room temperature a gum separated. The mother liquor was discarded and the gum was dissolved in water (2 L) with sufficient sodium hydroxide to complete solution. The solution was acidified with hydrochloric acid and acetic acids, treated with decolorizing charcoal and filtered. The filtrate was then strongly acidified with hydrochloric acid, which caused the separation of an apparently amorphous granular solid. This was filtered off, digested 0.5 h with hot ethanol (500 ml) collected, washed with ethanol and dried at 110°C. Yield of crude 5,5-(adipoylidimino)-bis[2,4,6-triiodo-N-methylisophthalamic acid].

**Trade Name**

- Myelotrust
  - Manufacturer: Winthrop
  - Country: -
  - Year Introduced: -

- Myelotrust
  - Manufacturer: Guerbet
  - Country: -
  - Year Introduced: -

- Iocarmic acid
  - Manufacturer: Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.
  - Country: -
  - Year Introduced: -

- Iocarmic acid
  - Manufacturer: Shanghai Lansheng Corporation
  - Country: -
  - Year Introduced: -

- Dimer-X
  - Manufacturer: Byk Gulden
  - Country: -
  - Year Introduced: -
The 5,5-(adipoyldiimino)-bis[2,4,6-triiodo-N-methylisophthalamic acid] was precipitated a second and third time from its sodium salt solution. The third precipitate was then dissolved in hot dimethylformamide (400 ml), and water (1.5 L) was slowly added. The mixture was digested and the hot mixture filtered, yielding a crystalline product which, after drying at 110°C, weighed 126.0 g (neutral equivalent, 724). This product was dissolved in dilute sodium hydroxide solution (1 L) and the solution was acidified (pH 5) and filtered into a hot stirred solution of hydrochloric acid (25 ml of concentrated acid in 75 ml water). The mixture was chilled and the solid collected, washed with water and dried at 110°C. Yield of 5,5-(adipoyldiimino)-bis[2,4,6-triiodo-N-methylisophthalamic acid] 114.0 g (45%). Melting point, 302°C (corrected), with decomposition.

References

Hoey G.B.; US Patent No. 3,290,366; Dec. 6, 1966; Assigned: Mallinckrodt Chemical Works, St. Louis, Mo., a corporation of Missouri

**IOCETAMIC ACID**

**Therapeutic Function:** Diagnostic aid

**Chemical Name:** Propanoic acid, 3-(acetyl(3-amino-2,4,6-triiodophenyl) amino)-2-methyl-

**Common Name:** Acide iocetamique; Acidum iocetamicum; Acidum jocetamicum; Iocetamic acid

**Structural Formula:**

![Structural Formula](image)

**Chemical Abstracts Registry No.:** 16034-77-8

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**Raw Materials**

m-Nitroaniline
Pyridine
Methacrylic acid
Sodium chloride
Manufacturing Process

A mixture of equimolecular amounts of m-nitraniline (69.0 g), methacrylic acid (43.0 g), and pyridine (39.5 g) was heated to 125°C for 20 h, and was then poured into 500 ml water. A semi-crystalline product separated from the liquid. The supernatant liquid was decanted and 500 ml fresh water was added. The pH was adjusted to 7-7.5 by means of sodium hydroxide. The precipitate was filtered with suction and washed with water. When the filtrate was acidified with acetic acid, a precipitate of N-(3-nitrophenyl)-β-amino-isobutyric acid was formed. When filtered, washed with water and dried, it weighed 56.0 g and had a melting point of 130°-131°C (recryst. from alcohol). The yield was 50% based on nitraniline.

0.25 mol (56.0 g) N-(3-nitrophenyl)-β-aminoisobutyric acid, prepared as described above, 160 ml glacial acetic acid, and 40 ml acetic anhydride were heated 48 h to 50°C, and the reaction mixture was poured into 600 ml water. A crystalline precipitate of N-acetyl-N-(3-nitrophenyl)-β-aminoisobutyric acid formed gradually. When recovered, it weighed 56.0 g (84% yield). Melting point 146°-148°C.

100.0 g N-acetyl-N-(3-nitrophenyl)-β-amino-isobutyric acid were dissolved in 1 L water and 40 ml 25% aqueous ammonia, and the solution was hydrogenated in the presence of about 10.0 g Raney nickel at 20°C and about 450 p.s.i. until the pressure drop indicated the complete conversion of the NO₂ groups to NH₂. Thus N-acetyl-N-(3-aminophenyl)-β-amino-isobutyric acid was obtained.

The solution of N-acetyl-N-(3-aminophenyl)-β-amino-isobutyric acid was filtered after standing overnight, mixed with an equal volume of acetic acid, and then after with a solution of 275.0 g iodine monochloride and 200.0 g sodium chloride in 1 L water. The mixture was kept at 50°C with stirring for 48 h. Light brown crystals of crude N-acetyl-N-(2,4,6-triiodo-3-aminophenyl)-β-amino-isobutyric acid precipitated, were filtered off, washed with water, and dried. They weighed 195.0 g (84.5% yield based on N-acetyl-N 3-nitrophenyl-p-amino-isobutyric acid).

References

Korver J.A.; US Patent No. 3,661,975; May 9, 1972
GB Patent No. 1,116,586; Nov. 25, 1965; Assigned: Dagra N.V. a limited liability company incorporated, Diemen Netherlands

IODAMIDE

Therapeutic Function: Diagnostic aid (radiopaque medium)
Chemical Name: 3-(Acetylamino)-5-[(acetylamino)methyl]-2,4,6-triiodobenzoic acid

Common Name: Ametriodinic acid

Structural Formula:

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Chemical Abstracts Registry No.: 440-58-4

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Raw Materials

3-Acetylaminomethyl-4-chloro-5-nitrobenzoic acid
Hydrogen
Potassium iodide dichloride
Acetic anhydride

Manufacturing Process

65.4 g (0.24 mol) 3-acetylaminomethyl-4-chloro-5-nitrobenzoic acid were dissolved in a mixture of 48 ml 10N sodium hydroxide and 1,800 ml water. 12 g of a 10% palladium catalyst on a carbon carrier were added, and the nitrobenzoic acid derivative was hydrogenated at slightly elevated temperature and at atmospheric pressure. The hydrogen was avidly absorbed. The nitro group was fully reduced to the corresponding amino radical within about 20 to 40 minutes, and 99 to 100% of the amount of chlorine ions to be theoretically expected was formed. Hydrogen absorption then stopped.

The catalyst was removed by filtration. The filtrate was diluted to about 18 liters, and was acidified with 15 ml concentrated hydrochloric acid. With vigorous stirring, 1,152 ml N KI\textsubscript{Cl\textsubscript{2}} solution were run into the diluted filtrate
over a period of about 20 to 30 minutes. A solid precipitate was formed, and was filtered off after about six hours. The solid material was washed with water, with sodium bisulfite solution, and again with water. It was dissolved in aqueous ammonium hydroxide solution, the solution was filtered, and the filtrate was acidified with concentrated hydrochloric acid containing a small amount of sodium bisulfite. After a short time, the precipitate formed was filtered with suction, washed with water, and dried.

There were obtained 109 g 3-acetylaminomethyl-5-amino-2,4,6-triiodobenzoic acid which decomposes and melts at approximately 230°C. The equivalent weight was determined experimentally as being 591, as compared to a theoretical value of 586.

A suspension of 40 g 3-acetylaminomethyl-5-amino-2,4,6-triiodobenzoic acid in 180 ml acetic anhydride were mixed with 0.4 ml concentrated sulfuric acid. An exothermic reaction was thereby initiated. Acetylation was completed by heating to 80°C for three hours. The reaction mixture was then evaporated to dryness in a vacuum at a temperature not exceeding 50°C. The residue was treated with a mixture of 30 ml concentrated aqueous ammonium hydroxide and 40 ml water, whereby the solid material dissolved with spontaneous heating. Within a few minutes, the ammonium salt of the acetylated product started precipitating. The precipitate and residual liquid were cooled externally with ice after about 15 minutes. The salt was separated from the liquid by filtration with suction, and was washed with ice cold saturated ammonium chloride solution.

The salt was dissolved in 300 ml water, and insoluble matter was removed from the solution by filtration. The free acid was precipitated from the filtrate at 50°C to 60°C by the addition of 40 ml 1:1 hydrochloric acid. The precipitate was filtered off after a few hours, washed with water, and dried. There were obtained 34 g 3-acetylaminomethyl-5-acetylamino-2,4,6-triiodobenzoic acid (79% of theoretical yield) having a melting point of 246°C to 248°C. The equivalent weight of this practically pure acid was found to be 631 as compared to the calculated value of 627.96.

When recrystallized from glacial acetic acid, the pure acid melts at 255°C to 257°C.

References
Merck Index 4878
Kleeman and Engel p. 493
I.N. p. 521
REM p. 1269

IODIPAMIDE

Therapeutic Function: Diagnostic aid (radiopaque medium)
**Chemical Name:** 3,3’-[(1,6-Dioxo-1,6-hexanediyl)diimino]bis[2,4,6-triodobenzoic acid]

**Common Name:** Adipodione

**Structural Formula:**

![Structural Formula](image)

**Chemical Abstracts Registry No.:** 606-17-7

**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
---|---|---|---
Cholografin | Squibb | US | 1954
Intralibix | Guerbet | France | 1955
Biligrafin | Schering | W. Germany | -
Endocistobil | Bracco | Italy | -
Endografin | Schering | W. Germany | -
Radio-Selectan Biliare | S.E.P.P.S. | France | -
Transbilix | Guerbet | France | -
Ultrabil | Spofa | Czechoslovakia | -

**Raw Materials**

2,4,6-Triodo-3-amino benzoic acid  
Adipic acid dichloride

**Manufacturing Process**

125 g of 2,4,6-triiodo-3-amino benzoic acid are dissolved in 250 cc of chlorobenzene and 15 g of adipic acid dichloride are added at a temperature between 110° and 130°C drop by drop to the solution. After evolution of hydrochloric acid (about 2 to 3 hours) has ceased, the precipitated crude adipic acid di-(3-carboxy-2,4,6-triiodo anilide) of the above formula is filtered hot with suction, washed with chlorobenzene, extracted by boiling with methanol and, for purification, dissolved in an amount of methanolic caustic soda solution required for neutralization, filtered with charcoal, and precipitated with dilute hydrochloric acid. Yield: 82.3 g, MP 306° to 308°C (with decomposition).

**References**

Merck Index 4890  
Kleeman and Engel p. 16
I.N. p. 46
REM p. 1265
Priewe, H. and Rutkowski, R.; US Patent 2,776,241; January 1, 1957; assigned to Schering AG, Germany

IODIXANOL

Therapeutic Function: Diagnostic aid

Chemical Name: 1,3-Benzenedicarboxamide, 5,5'-(2-hydroxy-1,3-propanediyl)bis(acetylimino))bis(N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-

Common Name: Iodixanol

Structural Formula:

Chemical Abstracts Registry No.: 92339-11-2

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Raw Materials

- Hydrochloric acid
- NaCl₂
- Sulfuric acid
- 2-Methoxyethanol
- Epichlorohydrin
- Dimethyl 5-nitroisophthalate
- 1-Amino-2,3-propandiol
- Sodium hydroxide
- Acetic anhydride

Manufacturing Process

Dimethyl 5-nitroisophthalate (215 g) and 1-amino-2,3-propandiol (196 g)
were refluxed in methanol (500 ml). After twenty hours the solution was cooled and stored in a refrigerator overnight. The product 5-nitro-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide was filtered and washed with methanol. Yield: 270 g (84%). M.p. 128-132°C.

5-Nitro-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide (18.1 g) was suspended in water (250 ml), conc. hydrochloric acid (4.2 ml) and 10% PdO/charcoal (0.5 g) were added, and the mixture hydrogenated in a Parr apparatus for one day. After filtration the filtrate was heated at 80-90°C and 3.88 M NaICl2 (42.5 ml) was added through a dropping funnel over 1 hour. The solution was heated for 2.5 hours. After cooling to 20°C 5-amino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide crystallized out.

5-Amino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide (110 g) was suspended in acetic anhydride (480 ml) and heated to 50°C. Concentrated sulfuric acid (3 ml) was then added. The starting material was dissolved after a few minutes, and the reaction mixture was heated at 60°C for 75 min. After cooling the residue dissolved in methanol (300 ml) with water (150 ml) the solution was heated to 50°C and the pH adjusted to about 10.5 by 10 N sodium hydroxide. After 4-5 hours the pH didn't decrease, and the hydrolysis was complete. The reaction mixture was cooled to 20°C and neutralized by adding hydrochloric acid. After stirring overnight 5-Acetamido-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide was filtered and washed with water. Yield: 94 g (80%). Melting point 275°C, dec.

2-Methoxyethanol (300 ml) and sodium hydroxide (20 g) was added to the reactor at 50°C, and 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophtalamide (304 g) was added after two hours of stirring. All solids were allowed to dissolve overnight before cooling to 30°C and adjustment to pH 12 with diluted hydrochloric acid. Epichlorohydrin (11 g) was added to the solution after further cooling to 15°C, and the reaction was allowed to proceed for 51 hours. As a result 1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropylaminocarbonyl)]-2,4,6-triodophenyl]-2-hydroxypropane was obtained.

References

Malthe-Sorensen D., et al.; US Patent No. 6,232,499 B1; May 15, 2001; Assigned to Nycomed Imaging AS, Oslo (NO)

IODOALPHIONIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 4-Hydroxy-3,5-diodo-α-phenylbenzenepropanoic acid

Common Name: Pheniodol
Structural Formula:

![Structural Formula Image]

Chemical Abstracts Registry No.: 577-91-3

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Raw Materials

- Dextro-β-(4-hydroxyphenyl)-α-phenylpropionic acid
- Iodine
- Dimethylaminoethanol
- Acetic acid

Manufacturing Process

Dextro-β-(4-hydroxyphenyl)-α-phenylpropionic acid (24 g) was dissolved in 630 ml of water containing 8.0 g of sodium hydroxide, and, with good stirring at 25°C, 51 g of iodine and 51 g of potassium iodide dissolved in 240 ml of water was added dropwise over a period of 30 minutes. During this period another 8 g of sodium hydroxide dissolved in 60 ml of water was added in order to keep the reaction mixture alkaline to phenolphthalein. Stirring was continued for 15 minutes longer. The resulting solution was made acid to Congo red with concentrated hydrochloric acid, and about 5 g of sodium bisulfite was added to partially decolorize the resulting slurry. The solid was collected by filtration and washed well with water.

The crude iodinated acid was then dissolved in 500 ml of 95% alcohol, 10 g of dimethylaminoethanol was added, the solution was decolorized with activated charcoal and filtered at 70°C. After keeping the filtrate for several hours at 5°C. the heavy crystalline precipitate which formed was collected by filtration and washed with acetone. The mother liquors were concentrated to 150 ml and cooled to give a second crop which was further purified by recrystallization from 50 ml of 95% alcohol. In this way a total of 36.0 g of dimethylaminoethanol salt of dextro-β-(3,5-diiodo-4-hydroxy)-α-phenylpropionic acid, MP 151° to 153°C, was obtained. The melting point of the dimethylaminoethanol salt of unresolved β-(3,5-diiodo-4-hydroxy)-α-phenylpropionic acid was 142° to 144°C.

The pure dimethylaminoethanol salt was dissolved in 400 ml of 50% acetic acid at 90°C and then cooled to 5°C. The solid which precipitated was
collected by filtration, washed with water, cold 50% acetic acid and finally with low-boiling petroleum ether. After drying in vacuo there was obtained 24 g of hydrated dextro-β-(3,5-diiodo-4-hydroxy)-α-phenylpropionic acid, MP 80° to 85°C.

References

Merck Index 4893
I.N. p. 756
Tullar, B.F. and Hoppe, J.O.; US Patent 2,552,696; May 15, 1951; assigned to Sterling Drug Inc.

IODOXAMIC ACID

**Therapeutic Function:** Diagnostic aid

**Chemical Name:** Benzoic acid, 3,3'-(1,16-dioxo-4,7,10,13-tetraoxahexadecane-1,16-diyl)diimino)bis(2,4,6-triiodo-)

**Common Name:** Acide iodoxamique, Acidum iodoxamicum, Iodoxamic acid

**Structural Formula:**

![Structural Formula of Iodoxamic Acid]

**Chemical Abstracts Registry No.:** 31127-82-9

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**Raw Materials**

4,7,10,13-Tetraoxahexadecane-1,16-dinitrile
Manufacturing Process

148.5 g 4,7,10,13-tetraoxahexadecane-1,16-dinitrile (U.S. Patent No. 2,401,607) was added to a solution of 232 g (2.45 mol) concentrate sulfuric acid in 290 ml absolute ethanol at 15°C. The mixture was heated at reflux for 15 hours, cooled and poured into 1000 g ice and 250 g ammonium sulfate. It was extracted with methylene chloride, dried and a solvent was removed in vacuum. The residue was distilled to give 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid dimethyl ester; BP: 190°-195°C/0.005 mm Hg.

1 mol above prepared diester was saponificated with equivalent of NaOH in water. The reaction mixture was heated for 90 minutes. On cooling it was extracted with ether and the water layer was evaporated to dryness. The residue was washed with acetone. The obtained disodium salt of 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid (yield 100%; MP: 102°-104°C) was acidified with calculated quantity of HCl to give the dicarbonic acid. The solvent was evaporated to dryness. Acetone was added to the residue for removing a by-product (sodium chloride) by filtration. Acetone was evaporated and the residue was extracted with ether, dried and evaporated. The residual liquid was 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid.

100 ml thionyl chloride was cautiously added to 56 g above prepared diacid and heated at 40°-50°C and excess thionyl chloride was distilled in vacuum. The residue was the 4,7,10,13-tetraoxahexadecane-1,16-dicarbonic acid dichloride. The desired iodoxamic acid was prepared from above dichloride and 3-amino-2,4,6-triiodobenzoic acid, in dimethylacetamide.

References

Felder and Pitre; D.B. Patent No. 1,937,211; July 22 1969; Milan, Italy

IOGLYCAMIC ACID

**Therapeutic Function:** Diagnostic aid (radiopaque medium)

**Chemical Name:** 3,3’-[Oxybis[(1-oxo-2,1-ethanediy1)imino]]bis[2,3,6-triiodobenzoic acid]

**Common Name:** -

**Chemical Abstracts Registry No.:** 2618-25-9
1930 Ioglycamic acid

**Structural Formula:**

![Structural Formula Image]

**Trade Name** | **Manufacturer** | **Country**   | **Year Introduced**
--- | --- | --- | ---
Biligram | Schering | W. Germany | 1971
Biligram | Schering | UK | 1972
Biligram | S.E.P.P.S. | France | 1974
Bilivistan | Schering | Italy | -
Rayvist | Schering | W. Germany | -

**Raw Materials**

- 2,4,6-Triiodo-aminobenzoic acid
- Diglycolic acid dichloride

**Manufacturing Process**

910 g of dry 2,4,6-triiodo amino benzoic acid are dissolved with stirring in 4,800 cc of dry, boiling chlorobenzene. A solution of 151.7 g diglycolic acid dichloride in 100 cc of dry chlorobenzene is slowly added to this solution and the mixture is further heated for 4 to 5 hours under reflux until development of hydrogen chloride has ceased. The resulting precipitate is filtered from the warm solution with suction and washed with chlorobenzene and then with ether. The microcrystalline, almost colorless crude product, 942 g, consists of the α-modification of diglycolic acid di-(3-carboxy-2,4,6-triiodo anilide).

The crude product is suspended, while stirring, in 2.5 liters of pure methanol and a solution of 73 g of pure sodium hydroxide in the same weight of water, diluted with 675 cc methanol, is slowly added to this suspension until the acid is dissolved and the pH of this solution reaches 9.0. The solution is allowed to stand at this pH for 15 minutes. The pH is then brought to 4.0 by addition of 10% acetic acid and 17 g of charcoal are stirred in. After 15 minutes the coal is filtered off and the clear filtrate is slowly added to a stirred solution of 415 cc of pure, concentrated hydrochloric acid in 4.15 liters of 50% methanol. After ½ hour of stirring and decanting after 1 hour, the precipitate is easily filtered off with suction, washed with little methanol and thoroughly with water, until the thixotropic residue is free of hydrochloric acid. In order to obtain a product of highest purity, this treatment is repeated two times. The resulting pure product, after drying in vacuo at 50°C still containing one molecule of methanol per two molecules of the acid (plus 4 molecules of water), must be suspended in boiling water and steamed out. The hot suspension is filtered with suction, the white microcrystalline residue is dried in vacuo at 50°C to give 860 g (83.5% of the theoretical yield) of the pure dihydrate of the diglycolic acid di-(3-carboxy-2,4,6-triiodo anilide), β-modification.
IOPAMIDOL

**Therapeutic Function:** Diagnostic aid (radiopaque medium)

**Chemical Name:** 5-(α-Hydroxypropionylamino)-2,4,6-triiodoisophthalic acid di-(1,3-dihydroxyisopropylamide)

**Common Name:** -

**Structural Formula:**

![Structural Formula of Iopamidol]

**Chemical Abstracts Registry No.:** 60166-93-0

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**Raw Materials**

- 5-Amino-2,4,6-triiodo-isophthalic acid
- Thionyl chloride
- DL-2-Acetoxypropionyl chloride
- 2-Amino-1,3-propanediol

**References**

Merck Index 4912
Kleeman and Engel p. 494
I.N. p. 28
Manufacturing Process

400 g (0.72 mol) 5-amino-2,4,6-triiodo-isophthalic acid was added to 200 ml thionyl chloride, the mixture was stirred at a boil for 6 hours, and the resulting solution was evaporated. The residue was dissolved in anhydrous ethyl acetate, and the solution was again evaporated to dryness. The solid material was dissolved in 4,000 ml ethyl acetate, and the solution was stirred into an ice-cold solution of 500 g sodium chloride and 200 g sodium bicarbonate in 2.5 liters water. The organic phase was separated from the aqueous solution, washed with aqueous sodium solution, dried by contact with anhydrous calcium chloride, and evaporated to dryness.

The residue of 420 g 5-amino-2,4,6-triiodo-isophthalyl chloride (97.5% yield) had a melting point above 300°C when recrystallized from toluene.

300 g (0.503 mol) 5-amino-2,4,6-triiodo-isophthalyl chloride was dissolved in 1,200 ml dimethylacetamide, and 187 g (126 mol) DL-2-acetoxypropionyl chloride was added dropwise to the solution with agitation. The mixture was permitted to stand overnight at ambient temperature and was then evaporated in a vacuum to approximately 400 ml. The oily residue was stirred into ice water to precipitate 353 g crystalline DL-5-(α-acetoxypropionylamino)-2,4,6-triiodo-isophthalyl chloride (98% yield) which was purified by suspension in warm chloroform free alcohol.

The purified intermediate melted at 210°C. 70.9 g (0.10 mol) of the intermediate was dissolved in 150 ml dimethylacetamide, and 15 g (0.08 mol) tributylamine was added. The mixture was heated to 50°C, and 56.6 g (0.62 mol) 1,3-dihydroxyisopropylamine (2-amino-1,3-propanediol) dissolved in 80 ml dimethylacetamide was added drop by drop. The reaction went to completion within a few hours, and the reaction mixture was evaporated to dryness in a vacuum. The oily residue was added to 350 ml methylene chloride with vigorous agitation, and the resulting precipitate was filtered off and purified by repeated suspension of warm methylene chloride.

Work-up of the reaction mixture yielded 56.5 g (73.5%) DL-5-α-hydroxypropionylamino-2,4,6-triiodo-isophthalic acid di-(1,3-dihydroxyisopropylamide) which was recrystallized from aqueous ethanol and melted with decomposition above 300°C.

References

Merck Index 4915
DFU 4 (12) 876 (1979)
I.N. p. 524

IOPANOIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)
Chemical Name: 3-Amino-α-ethyl-2,4,6-triiodobenzenepropanoic acid

Common Name: -

Structural Formula:

![Chemical Structure](image)

Chemical Abstracts Registry No.: 96-83-3

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Raw Materials

- m-Nitrobenzaldehyde
- Butyric anhydride
- Hydrogen
- Iodine monochloride

Manufacturing Process

(A) Preparation of α-Ethyl-m-Nitrocinnamic Acid: This acid is prepared from 100 g of m-nitrobenzaldehyde, 210 g of butyric anhydride and 73 g of sodium butyrate. The crude α-ethyl-m-nitrocinnamic acid is crystallized from ethanol giving about 105 g, MP 140° to 142°C. From the filtrates there may be isolated a small amount of a stereoisomer, which when pure melts at 105° to 106°C.

(B) Preparation of m-Amino-α-Ethylhydrocinnamic Acid: A mixture of 50 g of α-ethyl-m-nitrocinnamic acid, 9.1 g of sodium hydroxide, 600 cc of water and 5 teaspoons of Raney nickel catalyst is shaken at 32°C in an atmosphere of
hydrogen at an initial pressure of 450 psi until the calculated amount of hydrogen is absorbed. The filtered solution is acidified with hydrochloric acid, made basic with ammonium hydroxide and again acidified with acetic acid. Upon concentration of this solution, an oil separates which crystallizes upon standing, giving about 20 g, MP 60° to 68°C. Complete evaporation of the filtrate and extraction of the residue of inorganic salts with ether gives about 20 g of additional material, MP 54° to 59°C. Recrystallization of the combined product from benzene petroleum ether gives about 35 g of m-amino-α-ethylhydrocinnamic acid, MP 67° to 70°C.

(C) Preparation of β-(3-Amino-2,4,6-Triiodophenyll-α-Ethylpropionic Acid: A solution of 5.0 g of m-amino-α-ethylhydrocinnamic acid in 100 cc of water containing 5 cc of concentrated hydrochloric acid is added over a period of ½ hour to a stirred solution of 3.2 cc of iodine monochloride in 25 cc of water and 25 cc of concentrated hydrochloric acid heated to 60°C. After addition is complete, the heating is continued for one hour longer at 60° to 70°C. A black oil separates which gradually solidifies. The mixture is then cooled and sodium bisulfite added to decolorize. Recrystallization of the product from methanol gives about 8 g, MP 147° to 150°C. The β-(3-amino-2,4,6-triiodophenyl)-α-ethylpropionic acid may be purified further by precipitation of the morpholine salt from ether solution and regeneration of the free amino acid by treatment of a methanol solution of the morpholine salt with sulfur dioxide. The pure amino acid has the MP 155° to 156.5°C.

References
Merck Index 4916
Kleeman and Engel p. 495
DOT 15 (7) 310 (1979)
I.N. p. 28
REM p. 1266
Chemical Abstracts Registry No.: 99-79-6

Raw Materials

Ethyl undecylenate
Iodobenzene

Manufacturing Process

60 volumes of ethyl undecylenate is introduced gradually at 7° to 8°C during 35 minutes to a well-cooled mixture of 52.5 parts of aluminum chloride and 150 volumes of iodobenzene. The mixture is decomposed with cracked ice and dilute hydrochloric acid. The iodobenzene layer is washed with sodium bisulfite solution and with water, and then distilled. The composition of matter having the probable formula, ethyl 4-iodophenyl-undecylate, is a colorless liquid boiling at 196° to 198°C/1 mm, and of specific gravity of 1.26/20°C.

References

Merck Index 4917
Kleeman and Engel p. 494
REM p. 1267
Strain, W.H., Plati, J.T. and Warren, S.L.; US Patent 2,348,231; May 9, 1944; assigned to Noned Corporation and Eastman Kodak Company

IOPHENOIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: α-Ethyl-3-hydroxy-2,4,6-triiodobenzenepropanoic acid

Common Name: Iophenoic acid; Teridax

Structural Formula:
Chemical Abstracts Registry No.: 96-84-4

Raw Materials

- Sodium propionate
- Propionic anhydride
- Potassium hydroxide
- Sodium amalgam
- m-Hydroxybenzaldehyde
- Hydrochloric acid
- Acetic acid
- Iodine monochloride

Manufacturing Process

A mixture of m-hydroxy-benzaldehyde, fused sodium propionate and of butyric anhydride was stirred and refluxed at heating. The mixture was then poured into water and acidified with hydrochloric acid. The organic material was extracted with chloroform, the chloroform was evaporated, and the residue stirred for one and 1.5 h with dilute potassium hydroxide solution. Acetic acid was added to make the solution almost neutral, but still slightly basic, the mixture was stirred with activated charcoal for about 15 min, filtered, and the filtrate acidified to Congo red with hydrochloric acid. A crystalline product was obtained upon cooling for several hours, and this was collected by filtration and recrystallized from water giving \(\alpha\)-ethyl-\(m\)-hydroxycinnamic acid.

A solution of \(\alpha\)-ethyl-\(m\)-hydroxycinnamic acid and potassium hydroxide in water was added to 3% sodium amalgam, and the mixture was stirred while heating on a steam bath for several hours. The mixture was then cooled, the mercury separated, and the reaction mixture was acidified and extracted with ether. The ether extracts were concentrated giving a residue containing \(\alpha\)-ethyl-\(\beta\)-(\(m\)-hydroxyphenyl)propionic acid.

\(\alpha\)-Ethyl-\(\beta\)-(\(m\)-hydroxyphenyl)propionic acid was dissolved in acetic acid. The solution was warmed on a steam bath, and water was added followed iodine monochloride. The mixture was stirred and heated for several hours, and water was then added to cause precipitation of the product. The semi-solid precipitate was triturated with a small amount of 95% alcohol, collected by filtration and washed with low boiling petroleum ether. Recrystallization from dilute alcohol, using charcoal for decolorization, gave \(\alpha\)-ethyl-\(\beta\)-(2,4,6-triiodo-3-hydroxyphenyl)propionic acid.

References

IOPRONIC ACID

**Therapeutic Function:** Diagnostic aid (radiopaque medium)

**Chemical Name:** 2-[[2-[3-(Acetylamino)-2,4,6-triiodophen-oxy]ethoxy]methyl]-butanoic acid

**Common Name:** -

**Structural Formula:**

![Structural Formula](https://via.placeholder.com/150)

**Chemical Abstracts Registry No.:** 37723-78-7

**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
--- | --- | --- | ---
Bilimiru | Bracco | Italy | 1974
Bilimiro | Byk Gulden | W. Germany | 1980

**Raw Materials**

- Sodium
- 3-Acetylamino-2,4,6-triiodophenol
- Sodium hydroxide
- Hydrogen chloride
- 3-(2-Iodoethoxy)-2-ethylpropionic acid ethyl ester

**Manufacturing Process**

A solution of 192 g 3-acetylamino-2,4,6-triiodophenol, sodium (0.35 mol) in 350 ml dimethylacetamide, was mixed with 107.5 g 3-(2-iodoethoxy)-2-ethylpropionic acid ethyl ester (0.35 mol) at 90°C with stirring over a period of about 20 to 30 minutes. Stirring was continued while the mixture was held at 95°C to 100°C for 16 hours. The solvent was then removed by distillation in a vacuum, and the residue was poured into 4,000 ml water. The solid precipitate formed was recovered and washed with water, dilute sodium carbonate solution, dilute sodium bisulfite solution, and again with much water. The ethyl ester was obtained in a yield of 220 g (90%). When recrystallized from 75% aqueous ethanol, it melted at 80°C to 86°C.

The ester (70 g, 0.1 mol) was saponified in a boiling mixture of 250 ml methanol and 250 ml water to which 100 ml N sodium hydroxide solution was added in small batches with stirring. The methanol was distilled from the saponification mixture, the residue was mixed with water and extracted with ethyl acetate. The aqueous phase was acidified with hydrochloric acid in the presence of sodium bisulfite.

The free acid gradually crystallized from the acidified solution in the amount of
42.4 g (63% yield). When recrystallized from 50% ethanol and from ethyl acetate, it melted at 130°C.

References

Merck Index 4919
I.N. p. 29
Felder, E. and Pitre, D.; US Patent 3,842,124; October 15, 1974; assigned to Bracco Industria Chimica, Societa per Azioni (Italy)

IOPYDOL

Therapeutic Function: Diagnostic aid

Chemical Name: 4(1H)-Pyridinone, 1-(2,3-dihydroxypropyl)-3,5-diiodo-

Common Name: Iopydol; Jopydolum

Structural Formula:

![Structural Formula](image)

Chemical Abstracts Registry No.: 5579-92-0

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Raw Materials

- 4-Pyridone
- Chloroiodide

Manufacturing Process

50 g 4-pyridone was dissolved in 300 ml 20% hydrochloric acid and slowly mixed with 180 g of chloroiodide in 200 ml 20% hydrochloric acid. Then the obtained dark solution was strong alkalized with sodium hydroxide. The solvent was removed to dryness and sodium salt diiod-4-pyridone was
obtained. It was dissolved in water, filtered and equivalent quantity of glacial acetic acid or hydrochloric acid was added to give 3,5-diiod-4-pyridone as a powder. 34.5 g 3,5-diiod-pyridone was dissolved in 100 ml 1 N NaOH by heating on a water bath and added to a 15 g of monochlorohydrine added. The mixture was heated on water bath before a dense pasty mass obtained. It was filtered off and treated with 1 N NaOH. The obtained 1-(2,3-dihydroxypropyl)-3,5-diido-4(1H)-pyridinone was recrystallized from diluted hydrochloric acid. MP: 161°C.

References

D.R. Patent No. 579,224; Dec. 30, 1930; I.G.Farbenindustrie Akt.-Ges. in Frankfurt a. M.

IOPTHALAMATE SODIUM

Therapeutic Function: Diagnostic aid

Chemical Name: Benzoic acid, 3-(acetylamino)-2,4,6-triiodo-5-((methylamino)carbonyl)-, monosodium salt

Common Name: Iothalamate sodium; Jodtalaminatrium; Sodium isothalamate

Structural Formula:

![Chemical Structure](attachment:image.jpg)

Chemical Abstracts Registry No.: 1225-20-3

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Raw Materials

- Methylamine
- Palladium on charcoal
- 5-Nitroisophthalic acid, dimethyl ester
- Iodine monochloride
Manufacturing Process

Normal aqueous sodium hydroxide (0.02 eq) was added at room temperature with rapid swirling to a solution of 5-nitroisophthalic acid, dimethyl ester, (4.8 g, 0.02 mole) in acetone-methanol (100 ml each). The clear solution immediately assumed a deep red-purple color which gradually lightened to a brown color over a 25-minute period. On standing overnight the solution lightened in color to a pale pink.

The solvent was evaporated, and the residue extracted with warm water (50 ml). The residue of unsaponified diester (0.23 g), 4.2%; m.p. 115°-117°C was filtered off, and the filtrate was acidified to precipitate the crude monomethyl ester of 5-nitroisotalic acid. Yield 3.4 g (75%). M.p. 170.5°-175.5°C.

The preparation was repeated on a larger scale with certain variations. Methanolic potassium hydroxide was substituted for the aqueous sodium hydroxide, and acetone was used as the solvent for the 5-nitroisophthalic acid, dimethyl ester. Yield, 78%. M.P. 175°-179°C (corrected).

Crude 5-nitroisophthalic acid, monomethyl ester (46.3 g, 0.21 mole) was dissolved in 35% aqueous methylamine solution (500 ml). On standing, the orange solution became blood red. The reaction mixture was evaporated overnight on the steam bath, the cool residue was treated with 50 ml of water and the solution was acidified with hydrochloric acid. A yellow precipitate of crude N-methyl-5-nitroisophthalamic acid was separated and dried (yield 41.5 g). This acid was redissolved in dilute ammonia solution and the resulting solution (pH 5.2) was treated with charcoal. Acidification of the treated solution yield a pale yellow product of neutral equivalent 213. A small portion (10 g) was recrystallized from 1:1 water-ethanol (300 ml) to yield orange N-methyl-5-nitroisophthalamic acid. M.p. 251°-252.5°C.

Crude N-methyl-5-nitrosophthalamic acid (11.2 g, 0.05 mole) was reduced with hydrogen in a low pressure hydrogenator. The solvent was anhydrous methanol (250 ml) and the catalyst was 5% palladium on charcoal slurried in 10 ml of water. After the theoretical quantity of hydrogen for reduction of the nitro group had been absorbed the solution was filtered to remove the catalyst and the solvent was evaporated under reduced pressure, leaving a white residue of crude 5-amino-N-methylisophthalamic acid. M.p. 227°-230°C (corrected).

The crude 5-amino-N-methylisophthalamic acid was dissolved in hydrochloric acid (100 ml concentrated acid and 100 ml of water) and this solution was diluted to 1 liter with water. Iodine monochloride (27.4 g of 95% ICI, 0.16 mole) in concentrated hydrochloric acid (30 ml) was added in one portion to the stirred solution maintained at 54°C. The solution was heated on a steam bath. After 2 hours the solution was diluted to 1.5 liters and after 3 hours titration of an aliquot indicated that 50% of the iodine monochloride had been consumed. Precipitation of a solid began after 33/4 hours of reaction (75°C). Intermittent heating and stirring was continued for 4 days, 10 g of 95% iodine monochloride was added during the third day. After 4 days, titration of an aliquot indicated that 96% of the theoretical quantity of iodine monochloride had been consumed. The precipitated solid was filtered off, washed with water and dried at 75°C under reduced pressure. Yield of 5-amino-2,4,6-triiodo-N-
methylisophthalamic acid 20.6 g. M.p. 266-268°C (dec.).

1.95 molar KCl₂ a solution (1144 ml, 2.22 moles) was added during 0.5 hour to a stirred suspension of 5-amino-N-methylisophthalamic acid (196 g, 1.01 moles) in 2.5 liters of water. After three hours of additional stirring, a solution of sodium hydroxide (88 g, 2.2 moles of NaOH in 200 ml of water) was added. Then, additional 1.95 molar KCl₂ solution (522 ml, 1.01 mole) was added during 0.5 hour. The reaction mixture was stirred overnight after which the crude product was collected and purified by conversion first to the ammonium salt, then to the free acid. Yield of 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, 310 g (53.6%).

Acetyl chloride (17 ml, 0.24 mole) was added in portions during 10 minutes to a stirred slurry of 5-amino-2,4,6-triiodo-N-methylisophthalamic acid (57.2 g, 0.1 mole) in dimethylacetamide (120 ml). Solution occurred in 0.5-1 hour and after a total of 1.5 hours 20 ml of water was added and the reaction mixture was evaporated to a thick slurry. The product was purified by twice dissolving it as a sodium salt and precipitating the free acid by the addition of mineral acid. The resulting nearly colorless 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid decomposed at about 285°C but did not melt below 300°C. Yield, 47 g (76.5%).

5-Acetamido-2,4,6-triiodo-N-methylisophthalamic acid was slurried in water and dissolved by the addition of an equivalent quantity of sodium hydroxide. The solution was evaporated to dryness to yield the sodium salt of 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid. Its solubility in water at 25°C is approximately 85 g per 100 ml of solution. The acute intravenous LD₅₀ of this salt in male albino mice is approximately 19.2 g/kg.

References

Iothalmate meglumine 1941

Iothalmate meglumine

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3-(Acetylamino)-2,4,6-triiodo-5-[(methylamino)carbonyl]-benzoic acid

Common Name: -

Chemical Abstracts Registry No.: 13087-53-1; 2276-90-6 (Acid)

Raw Materials

5-Amino-2,4,6-triiodo-N-methylisophthalamic acid
Acetic anhydride
N-Methyl glucamine
Crude 5-amino-2,4,6-triiodo-N-methylisophthalamic acid (21.0 g) was dissolved in warm dimethylacetamide (40 ml) and acetic anhydride (30 ml) and concentrated sulfuric acid (2 drops) were added. This solution was heated on the steam bath for 2 hours, then heated at 110°C for 5 minutes, then cooled. Water and ammonium hydroxide were added to destroy the excess acetic anhydride, after which the mixture was evaporated to a volume of 50 ml. The cooled solution was acidified with concentrated hydrochloric acid and a tan solid was collected. The crude product was dissolved in 100 ml of water containing a slight excess of sodium hydroxide. The pH was adjusted to 4.5 with acetic acid, and the solution was treated with charcoal. The colorless solution was acidified with concentrated hydrochloric acid and cooled, and the precipitate was filtered off and dried under reduced pressure. The resulting 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid decomposes about 285°C and does not melt below 300°C.

5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid was slurried in water and dissolved by the addition of an equivalent quantity of N-methylglucamine. The solution was evaporated to dryness to yield the meglumate salt of 5-acetamido-2,4,6-triiodo-N-methylisophthalamic acid.
IOTHIOURACIL

**Therapeutic Function:** Thyroid inhibitor

**Chemical Name:** 2,3-Dihydro-5-iodo-2-thioxo-4(1H)-pyrimidinone

**Common Name:** Iodothiouracil

**Structural Formula:**

![Structural Formula](image)

**Chemical Abstracts Registry No.:** 5984-97-4

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**Raw Materials**

- 5-Iodo-2-benzyl thiouracil
- Acetic anhydride

**Manufacturing Process**

As an illustrative example 64.4 g of 5-iodo-2-benzyl thiouracil were deposited in the reaction vessel and dissolved by adding 400 cc of glacial acetic acid containing 10 cc of acetic anhydride and the reaction vessel was connected tightly with the reflux condenser. The second vessel or generator was charged with 95 cc of acetic anhydride and the vessel connected to a vessel such as a dropping funnel or equivalent containing 75 cc of a 50% solution of hydroiodic acid which was added slowly, as by dropwise addition, to the acetic anhydride in the generator. The mixture in the generator soon became hot and the hydrogen iodide which evolved passed continuously through the connecting conduit into the reaction flask just above the level of liquid therein. As the hydrogen iodide contacted the solution of the 2 benzyl derivative, a ring of the debenzylated product formed under the inlet conduct. This operation was continued until all of the hydroiodic acid was added to the generator vessel. The hydrogen iodide remaining in the generator was driven over into the reaction vessel by heating the generator. It was ascertained that the reaction is complete when no more precipitate forms in the main reaction vessel. During the reaction vapors evolved were condensed in the condenser and returned to the reaction vessel as reflux. The upper end of the reflux is
preferably connected with a vent leading to a drying chamber.

The reaction vessel was cooled and the precipitate separated by pouring or decanting off the supernatant liquor. The precipitate of the 5-iodo-2-thiouracil was then thoroughly washed, as, for example, on a Buchner funnel. The precipitate was then extracted twice with hot glacial acetic acid to remove unreacted material and then washed thoroughly by alternate washes with alcohol and water. The product was then further purified by dissolving it in warm dilute sodium hydroxide and after cooling was reprecipitated by careful acidulation with acetic acid. Utilizing this procedure 37 g of purified 5-iodo-2-thiouracil were obtained.

The supernatant liquid separated from the precipitate was concentrated in vacuo and 7.4 g of the unreacted 5-iodo-2-benzyl thiouracil were recovered. This obviously may be utilized for further debenzylation.

As pointed out previously, the 5-iodo-2-thiouracil is carefully dried, preferably in a vacuum over P₂O₅.

References

Merck Index 4924
OCDS Vol. 1 p. 265 (1977)
I.N. p. 573
Barrett, H.W.; US Patent 2,585,615; February 12, 1952; assigned to The Chemical Foundation

IOTROXIC ACID

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3,3'-[Oxybis(ethyleneoxymethylene)carbonylimino)]bis-[2,4,6-triiodo-benzoic acid]

Common Name: -

Structural Formula:

![Structural Formula Image]

Chemical Abstracts Registry No.: 51022-74-3
Raw Materials

3-Amino-2,4,6-triiodobenzoic acid
3,6,9-Trioxaundecane diacid dichloride

Manufacturing Process

(a) Condensation in dimethylacetamide: To a suspension of 51.5 g of anhydrous 3-amino-2,4,6-triiodo-benzoic acid (0.1 mol) in 100 ml of dimethylacetamide were slowly added dropwise, while stirring, 15.5 g of 3,6,9-trioxaundecanediacid dichloride (0.06 mol), during which the temperature gradually rose to about 50°C and the whole passed into solution. After being stirred overnight, the solution was added dropwise to 1 liter of a 0.28 N solution of sodium hydroxide, and then 200 ml of 2 N hydrochloric acid were cautiously added. The precipitate was filtered off with suction, washed with water and dried. The yield was practically quantitative.

(b) Condensation in dioxan: 15.5 g of 3,6,9-trioxaundecane diacid dichloride were added dropwise at about 95°C to a solution of 51.5 g of anhydrous 3-amino-2,4,6-triiodo-benzoic acid in 52 ml of anhydrous dioxan. After further stirring and heating for 3 hours, the solution was cooled, stirred dropwise into 500 ml of a 0.4 N solution of sodium hydroxide, and further worked up as described in paragraph (a). The yield was practically quantitative.

(c) Purification: To the crude product obtained as described under paragraph (a) or (b) in 300 ml of methanol was slowly added a quantity (about 15 ml) of a 12 N solution of sodium hydroxide such that a test portion diluted with water had a pH-value of 8 to 9. After stirring the mixture overnight, the sodium salt of 3,6,9-trioxaundecane-1,11-dioyl-bis-(3-carboxy-2,4,6-triiodo-anilide) which crystallized out was filtered off with suction, was hed with methanol and dried. Yield: 92 g (90% of the theoretical yield).

A solution of the salt in 900 ml of water was treated with active carbon, and concentrated hydrochloric acid was added until the pH-value was 1. The precipitate was filtered off with suction, washed with water, and dried at 50°C. The yield of pure 3,6,9-trioxaundecane-1,11-dioyl-bis-(3-carboxy-2,4,6-triiodo-anilide) was 80 g (80% of the theoretical yield). The substance melted at 175°C with sintering.

References

Kleeman and Engel p. 497
DOT 15 (1) 48 (1979)
I.N. p. 30
Schering, A.G.; British Patent 1,501,507; February 15, 1978
IOXITALAMIC ACID

Therapeutic Function: Diagnostic aid

Chemical Name: 3-(Acetylamino)-5-(((2-hydroxyethyl)amino)carbonyl)-2,4,6-triiodobenzoic acid

Common Name: Acide ioxitalamique; Acidum ioxitalamicum; Acidum joxitalamicum; Ioxitalamic acid

Structural Formula:

![Structural Formula](image)

Chemical Abstracts Registry No.: 28179-44-4

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Raw Materials

- Acetic acid
- Hydrochloric acid
- NaICl₂
- Thionyl chloride
- Sodium hydroxide
- Sulfuric acid
- Triethylamine
- Ammonia
- 3-Methoxycarboxyl-5-nitrobenzoic acid
- Ammonium chloride
- Palladium oxide on charcoal
- Sodium bicarbonate
- Acetic anhydride
- Ethanolamine

Manufacturing Process

3-Methoxycarboxyl-5-nitrobenzoic acid (25 g) was hydrogenated in methanol (500 ml) using palladium oxide on charcoal (2.5 g 10%) at atmospheric pressure. When the exothermic reaction was completed the catalyst was fluttered off. After cooling the solution at -20°C for 2.5 h, 12.7 g of 3-amino-5-methoxycarbonylbenzoic acid was isolated. An additional 6.5 g of it was isolated by concentrating the mother liquor.

The 3-amino-5-methoxycarbonylbenzoic acid (12.0 g) was suspended in water (280 ml), dissolved by addition of concentrated hydrochloric acid (7.1 ml) and glacial acetic acid (28.5 ml). At 60°-70°C NaICl₂ solution (73 ml, 58.7 g ICl/100 ml) was added dropwise while stirring in the course of about 3 h. The reaction mixture was heated at 80°-90°C for additional 3 h while stirring.
After cooling to room temperature the mother liquor was decanted and the residue dissolved as ammonium salt in water (80 ml). The ammonium salt was precipitated by adding ammonium chloride (2.4 g) and cooling to 0°C. The ammonium salt was filtered off and dissolved in water (140 ml), charcoaled twice at 80°C and the acid was precipitated at room temperature by addition of hydrochloric acid and was filtered off. The crude product was dissolved in ethyl acetate (100 ml) and the solution was washed 3 times with hydrochloric acid (2 N). By evaporating the solvent, 19 g of 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoic acid was isolated. Melting point 170°-176°C.

A mixture of 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoic acid (198 g) and thionyl chloride (400 ml) was heated while stirring at 70°C for 16 h. The solid material dissolved slowly. Thionyl chloride was evaporated in vacuo, the residue dissolved in chloroform (1000 ml), the solution washed with water (80 ml each), twice with saturated sodium bicarbonate, then 5 times with 2 N sodium hydroxide solution and finally with water to neutral. The solution was dried with CaCl₂ filtered and evaporated to dryness. The 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride was dried at 50°C in vacuo. Yield: 203.0 g. Melting point 55°-60°C.

To the 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride (53.0 g) was added acetic anhydride (106 ml). After stirring at room temperature for 20 min then insoluble material was filtered off (3-4 g). To the filtrate was added concentrated sulfuric acid (0.3 ml) whereby a yellowish product started to precipitate. The temperature reached about 50°C. The 3-acetamido-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride was isolated after storing in refrigerator overnight. Yield: 39.0 g. Melting point 210°-215°C.

The 3-acetamido-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride was dissolved in a mixture of dioxan and dimethylformamide. In the course of 2 h this solution was added dropwise to a solution of ethanolamine and triethylamine in dioxan. The stirring was continued. A sticky precipitate was filtered off. The filtrate was evaporated to dryness in vacuo. The residue was triturated with aqueous sodium bicarbonate, filtered off and mixed with first fraction. The combined solids were then suspended in aqueous sodium bicarbonate filtered off washed with water and dried in vacuo to give methyl 5-acetamido-2,4,6-triiodo-(N-β-hydroxyethyl)-isophthalamate.

The methyl 5-acetamido-2,4,6-triiodo-(N-β-hydroxyethyl)-isophthalamate was mixed with fresh distilled ethanolamine and stirred. The excess ethanolamine was removed in vacuo at 50°-60°C. The residue was dissolved in water, and charcoaled at pH 5.5. The crude product was precipitated with hydrochloric acid (pH 0.5) and filtered after stirring at 0°C. 5-Acetamido-2,4,6-triiodo-(N-β-hydroxyethyl)isophthalamic acid was suspended in ethanol and dissolved by addition of concentrated ammonia. The ammonium salt started to precipitate in the course and was isolated after stirring. The salt was dissolved in water, filtered and the acid was precipitated with hydrochloric acid (pH 0.5). After stirring the product was filtered off and dried in vacuo.

References

IPRATROPIUM BROMIDE

**Therapeutic Function:** Bronchodilator

**Chemical Name:** 3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide

**Common Name:** -

**Structural Formula:**

![Structural Formula](image)

**Chemical Abstracts Registry No.:** 22254-24-6

**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
--- | --- | --- | ---
Aatrovent | Boehringer Ingelheim | W. Germany | 1975
Aatrovent | Boehringer Ingelheim | UK | 1977
Aatrovent | De Angeli | Italy | 1980
Brevia | Valeas | Italy | 1980
Aatrovent | Teijin | Japan | 1981
Aatrovent | Boehringer Ingelheim | Canada | 1982
Atem | Chiesi | Italy | -
Itrop | Boehringer Ingelheim | - | -
Vagos | Valeas | Italy | -

**Raw Materials**

- N-Isopropyl-noratropine
- Methyl bromide

**Manufacturing Process**

21 1.5 g (0.667 mol) of N-isopropyl-noratropine were dissolved at 60°C in 2.11 liters of absolute toluene in a 3-liter glass pressure tube. While the solution was still warm, 95 g (1 mol) of ice-cold methylbromide were added, and the pressure tube was sealed immediately thereafter. The reaction mixture was kept at 60°C for four days. After one hour of standing, the formation of crystals began. At the end of four days the crystals were separated by vacuum filtration at 60°C, washed with 600 cc of toluene at 60°C, and dried in vacuo in a drying cabinet at 100°C. Raw yield: 263.7 g (95.8% of theory). MP: 224°C to 225°C (decomp.). The raw product was refluxed with 2.5 liters of chloroform for 30 minutes, vacuum filtered while
hot, washed with 200 cc of chloroform, and dried in a vacuum drying cabinet at 100°C. Yield: 249 g (90.6% of theory). MP: 226°C to 228°C (decomp.). The purified product was recrystallized from 1.2 liters of n-propanol, washed with 200cc of n-propanol and dried in a vacuum drying cabinet at 100°C. Yield: 237 g (86.15% of theory). MP: 230°C to 232°C (decomp.). By evaporation of the mother liquor to 100 cc another 6.0 g of the pure product, MP 230°C to 231.5°C (decomp.), were obtained.

References

Merck Index 4929
Kleeman and Engel p. 498
DOT 11 (12) 461 (1975) and 17 (7) 299 (1981)
I.N. p. 525

**IPRONIAZID**

**Therapeutic Function:** Antidepressant, Monoamine oxidase inhibitor

**Chemical Name:** 4-Pyridinecarboxylic acid 2-(1-methylethyl)hydrazide

**Common Name:** -

**Structural Formula:**

![Structural Formula](image)

**Chemical Abstracts Registry No.:** 54-92-2

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Raw Materials

Isonicotinyl hydrazide
Acetone
Hydrogen

Manufacturing Process

A mixture of 40 g of isonicotinyl hydrazine and 600 cc of acetone was heated on a steam bath until solution was complete. Upon cooling the reaction mixture, 1-isonicotinyl-2-isopropylidene hydrazine precipitated in the form of white needles; MP 161°C to 161.5°C.

A solution of 20 g of 1-isonicotinyl-2-isopropylidene hydrazine in 150 cc of methanol was reduced with hydrogen at room temperature and 50 psi using 300 mg of platinum black as a catalyst.

References

Merck Index 4934
Kleeman and Engel p. 499
OCDS Vol. 1 p. 254 (1977)
I.N. p. 525

IPRONIDAZOLE

Therapeutic Function: Antiprotozoal

Chemical Name: 1-Methyl-2-(1-methylethyl)-5-nitro-1H-imidazole

Common Name: 2-Isopropyl-1-methyl-5-nitroimidazole

Structural Formula:

![Chemical Structure Image]

Chemical Abstracts Registry No.: 14885-29-1

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Raw Materials

2-Isopropyl-4-nitroimidazole
Dimethyl sulfate

Manufacturing Process

2-Isopropyl-4 (or 5-nitroimidazole) (31 g = 0.2 mol), dioxane (70 g) and dimethylsulfate (28 g = 0.22 mol) were heated on a steam bath under reflux for 45 minutes. The solvent was removed in vacuo on a steam bath, the residue dissolved in 20 ml of water and the product precipitated by the gradual addition of 80 g of 25% sodium hydroxide solution at 0°C. A small additional amount was obtained by extraction of the mother liquor with methylene chloride. The product melted at 60°C.

The product was purified as follows. 60 g of product was dissolved in 3N aqueous hydrochloric acid, the solution was treated with charcoal and filtered. The filtrate was neutralized by the gradual addition of aqueous concentrated ammonia at 0°C to 5°C under stirring whereupon the product precipitated in white plates as the neutralization proceeded. The precipitate was filtered by suction, washed on the filter with 50 ml of ice cold water and dried at room temperature, MP 60°C.

The hydrochloride salt was formed by reacting the product, dissolved in isopropanol, with 25% ethanolic hydrochloric acid, whereupon the salt precipitated and was isolated. It has a melting point of 177°C to 182°C (dec). Similarly, the bisulfate salt was formed using 96% sulfuric acid. It has a MP of 151.5°C to 152.5°C.

References

Merck Index 4934
OCDS Vol. 2 p. 244 (1980)
I.N. p. 525

IRBESARTAN

Therapeutic Function: Antihypertensive

Chemical Name: 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-

Common Name: Irbesartan

Chemical Abstracts Registry No.: 138402-11-6
Structural Formula:

![Structural Formula Image]

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**Raw Materials**

- Ethyl valerimidate
- Sodium cyanide
- Triethylamine
- Valeryl chloride
- Tributyltin azide
- 1-Aminocyclopentanecarboxylic acid
- Cyclopentanone
- Oxalic acid dihydrate
- 4-Bromomethyl-2'-cyanobiphenyl
- Trityl chloride

**Manufacturing Process**

1. Synthesis of 2-n-Butyl-4-spirocyclopentane-2-imidazolin-5-one

Method 1:

The ethyl ester of 1-aminocyclopentanecarboxylic acid is prepared according to Adkins and Billica (J. Amer. Chem. Soc., 1948, 70, 3121).

Ethyl valerimidate hydrochloride is prepared according to Mac Elvain (J. Amer. Chem. Soc., 1942, 64, 1825-1827) and then freed from its hydrochloride by reaction with potassium carbonate and extraction with CH₂Cl₂.
The ethyl ester of 1-aminocyclopentanecarboxylic acid (1.57 g) and ethyl valerimidate (1.56 g) are dissolved in 12 ml of xylene containing 6 drops of acetic acid. After refluxing for 6.5 h, the reaction medium is concentrated under vacuum, the residue is chromatographed on silica gel using a chloroform/methanol/acetic acid mixture (94/4/2; v/v/v) as the eluent. The fraction containing the expected product is evaporated several times in the presence of xylene and then benzene in order to remove the acetic acid. 1.91 g of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one are obtained in the form of a thick oil.

Method 2:

1.97 g of sodium cyanide are dissolved in 3.9 ml of water in a round-bottomed flask and a solution containing 2.33 g of ammonium chloride in 5.9 ml of water and 3.5 ml of 20% aqueous ammonia is added; finally, 3 g of cyclopentanone in 3.8 ml of methanol are added to the flask. After stirring for 1.5 h, the mixture is heated at 60°C for 45 min, heating is then stopped, stirring is continued for 45 min and the mixture is then cooled to 25°C. It is extracted several times with methylene chloride.

The 1-aminocyclopentanenitrile obtained is dissolved in 300 ml of acetone, and a solution of 2.25 g of oxalic acid dihydrate in 200 ml of acetone is added, with stirring. The precipitate of 1-aminocyclopentanenitrile formed is filtered off.

5.1 g of the oxalate obtained in the previous step are treated with 7.65 ml of concentrated sulfuric acid (d = 1.84) over 45 min, with stirring. The evolution of a gas is observed and the temperature rises to 100°C. The mixture is cooled to about 35°C and poured into a mixture of ice and concentrated aqueous ammonia (10 g/2.8 ml). The suspension formed is extracted with chloroform containing 5% of methanol. The 1-aminocyclopentanecarboxamide was obtained.

3 g of the compound prepared in the previous step are placed in 70 ml of anhydrous THF and 3.3 ml of triethylamine, and 3 ml of valeryl chloride in 10 ml of anhydrous THF are added, with stirring. A white suspension is formed. The intermediate which is formed, but not isolated, is 1-(N-valeryl)aminocyclopentanecarboxamide. 6 g of potassium hydroxide pellets, 7 ml of water and 16 ml of methanol are added. The mixture is refluxed for 2.5 h and 9 g of ammonium chloride are then added. After stirring for 15 min, the mixture is concentrated under vacuum. The residue of the 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one obtained is taken up in water and extracted with ethyl acetate.

2. Synthesis of 2-n-butyl-4-spirocyclopentane-1-[(2’-(tetrazol-5-yl)biphenyl-4-yl)-methyl]-2-imidazolin-5-one

A mixture containing 250 mg of sodium hydride (as an 80% dispersion in mineral oil) and 5 ml of DMF is prepared under a nitrogen atmosphere and a solution containing 0.97 g of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one in 10 ml of DMF is added dropwise. The mixture is stirred for 30 min at 20°C and a solution of 1.5 g of 4-bromomethyl-2'-cyanobiphenyl in 10 ml of DMF is then added. After stirring for 1 h at 20°C, the DMF is evaporated off under reduced pressure, the residue is then taken up with ethyl acetate,
filtered and evaporated. The residue of 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one is purified by chromatography.

1.56 g of the previous product, 2.6 g of tributyltin azide and 30 ml of xylene are refluxed for 66 h. The xylene is then evaporated off and the residue is dissolved in 20 ml of CH$_2$Cl$_2$ and 5 ml of THF with the addition of 0.8 ml of 10 N sodium hydroxide solution and, after stirring for 30 min, 2.5 g of trityl chloride, and the mixture is stirred for 26 h. After evaporation of the solvents, the residue is taken up in ethyl acetate in ethyl acetate, washed with water and then with a 3% solution of potassium bisulfate and water. It is dried and evaporated. The residue is chromatographed on alumina using a hexane/ethyl acetate mixture (9/1; v/v) as the eluent to give 1.97 g of the 2-n-butyl-4-spirocyclopentane-1-[(2'-(triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one. Melting point 150-152°C.

1.96 g of the product prepared in the previous step are dissolved in 10 ml of methanol and 10 ml of THF. After the reaction medium has been cooled to 5°C, 1.5 ml of 4 N hydrochloric acid are added and the mixture is stirred for 3 h at 20°C and 1 h at 30°C. After evaporation of the solvents, the residue is taken up in water and the pH is brought to 12 by the addition of 10 N sodium hydroxide solution. The aqueous phase is extracted with ether, toluene and ether again. The aqueous phase is acidified to pH 2 by the addition of 1 N hydrochloric acid and then extracted with ethyl acetate and the extract is evaporated. The aqueous phase is acidified to pH 2 by the addition of 1 N hydrochloric acid and then extracted with ethyl acetate and the extract is dried and evaporated. The white solid obtained is dried at 50°C under 0.05 mm of mercury to give 840 mg of the 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one. Melting point 180-181°C.

References

IRINOTECAN HYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: (1,4'-Bipiperidine)-1'-carboxylic acid, (4S)-3,4,12,14-tetrahydro-4,11-diethyl-4-hydroxy-3,4-dioxo-1H-pyrano(3',4':6,7)indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride

Common Name: Camptetin hydrochloride; Irinotecan hydrochloride

Chemical Abstracts Registry No.: 100286-90-6
Structural Formula:

![Structural Formula Image]

### Trade Name

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### Raw Materials

- Triethylamine
- 7-Ethyl-10-hydroxycamptothecin
- Phosgene dimer
- 1-Chlorocarbonyl-4-piperidinopiperidine
- 4-Piperidinopiperidine

### Manufacturing Process

7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carboxyloxy camptothecin was synthesized by 2 methods.

**Method 1.**

7-Ethyl-10-hydroxycamptothecin (500 mg, 1.27 mmol) was suspended in dry dioxane (400 ml) and dissolved therein by adding triethylamine (2 ml) to the suspension under warming. This solution was stirred at room temperature while introducing thereinto phosgene prepared toties quoties by decomposing phosgene dimer (trichloromethoxychloroformate, 400 ml) in the presence of an active carbon catalyst. After 0.5 hours, consumption of the starting materials was confirmed and insoluble 10-chlorocarbonyloxy-7-ethylcamptothecin was removed by filtration.

10-Chlorocarbonyloxy-7-ethylcamptothecin (300 mg, 0.66 mmol) is suspended in dry dioxane (50 ml). To this suspension is added 4-piperidinopiperidine (330 mg, 1.96 mmol) as the amine, the reaction followed by the after-treatment was carried out whereby the 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carboxyloxy camptothecin title compound (154 mg, 39.8%) was obtained.
Method 2.

7-Ethyl-10-hydroxycamptothecin (790 mg, 2.01 mmol) and 1-chlorocarbonyl-4-piperidinopiperidine (910 mg, 3.95 mmol) were dissolved in anhydrous pyridine (50 ml), and the mixture was stirred for 1 hour at 20°C. The reaction mixture was evaporated to dryness in vacuo, the residue was dissolved in CHCl₃ (200 ml). The solution was washed successively with a 7% aqueous solution of NaHCO₃ (200 ml), a saturated aqueous solution NaCl, and the CHCl₃ layer was filtered, and evaporated in vacuo. The residual material was decolorized by passing it through a short silica gel column. 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin was obtained as a pale yellow mass, which was recrystallized from ethanol (ca. 60 ml) to give colorless needles (750 mg, 63.5% in yield).

To an ice-cooled suspension in distilled water (15 ml) of 7-ethyl-10-[1-(4-piperidino)piperidino]carbonyloxycamptothecin (1.00 g, 1.7 mmol) was added 0.1 N HCl (15.3 ml, 1.53 mmol), and the suspension was stirred vigorously for 5 minutes under cooling in an ice bath and filtered off. 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin hydrochloride was obtained in yield 96%.

References

Miyasaka T. et al.; US Patent No. 4,604,463; August 5, 1986; Assigned to Kabushiki Kaisha Yakult Honsha, Tokyo, Japan

ISAXONINE PHOSPHATE

Therapeutic Function: Neurotropic

Chemical Name: N-(1-Methylethyl)-2-pyrimidinamine

Common Name: -

Structural Formula:

Chemical Abstracts Registry No.: 4214-72-6 (Base)

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Raw Materials

2-Isopropylamino pyrimidine
Phosphoric acid

Manufacturing Process

6 liters of ethanol and 685 g (5 mold of 2-isopropylamino pyrimidine were added to a 10 liter reactor and stirred. To the solution were added 600 g (5.2 mols) of phosphoric acid and the mixture was boiled under reflux for one hour. There was obtained a dark green solution which was treated with 30 g of carbon black. After separation and crystallization while stirring overnight, the crystallized product was separated, washed with ethanol and dried at 50°C. There was obtained 1,027 g (87% yield) of a white powder melting at 125°C. The analysis of the compound showed a good correspondence with the formula C₇H₁₄O₄N₃P.

References

Merck Index 4953
DFU 1 (5) 315 (1982)
Eesanu, A.; US Patent 4,073,895; February 14, 1978; assigned to Societe D'Etudes de Produits Chimiques (France)

ISOAMINILE

Therapeutic Function: Antitussive

Chemical Name: α-[2-(Dimethylamino)propyl]-α-(1-methylethyl) benzeneacetonitrile

Common Name: -

Structural Formula:

Chemical Abstracts Registry No.: 77-51-0

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Raw Materials

α-Isopropyl phenyl acetonitrile
Sodium amide
2-Dimethylamino-1-chloropropane

Manufacturing Process

140 cc of benzene and 24 g of α-isopropyl phenyl acetonitrile are added to 7.5 g of sodium amide. The mixture is stirred and refluxed for one hour. After cooling, 25 g of 2-dimethylamino-1-chloropropane, dissolved in 20 cc of benzene, are added and stirring and refluxing of the mixture is continued for 4 hours. After the reaction is completed, water is added to the reaction mixture. The benzene layer is separated from the aqueous layer and is extracted by means of 4N hydrochloric acid. The acid solution is rendered alkaline.

The separated oil is taken up in ether. After drying the ethereal solution over sodium sulfate and distilling off the ether, the resulting crude α-isopropyl-α-(β'-dimethylamino propyl) phenyl acetonitrile is purified by distillation in a vacuum. The compound boils at 138° to 146°C/3 mm, according to US Patent 2,934,557.

References

Merck Index 4956
Kleeman and Engel p. 499
OCDS Vol. 1 p.82 (1977)
I.N. p. 527
Stuhmer, W. and Funke, S.; US Patent 2,934,557; April 26, 1960; assigned to Kali-Chemie AG, Germany

ISOBORNYL THIOCYANOACETATE

Therapeutic Function: Pediculicide

Chemical Name: Thiocyanatoacetic acid 1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl ester

Common Name: -
Structural Formula:

![Structural Formula](image)

Chemical Abstracts Registry No.: 115-31-1

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Raw Materials

Camphene  
Chloroacetic acid  
Potassium thiocyanate

Manufacturing Process

200 g of camphene and 150 g of chloroacetic acid were heated 16 hours at 125°C, cooled to room temperature and the resulting product washed with water. In this way, 177 g of isobornyl monochloroacetate, analyzing 12.8%, by weight, chlorine was recovered. 174 g of the isobornyl monochloroacetate was dissolved in 300 cc of ethyl alcohol, 100 g of potassium thiocyanate added to this solution and the mixture refluxed for a period of 8 hours. 276 g of a product was recovered, which analyzed as follows: chlorine, 0.2% by wt. and sulfur, 10.9% by wt. This analysis shows the product to be principally isobornyl thiocyanoacetate.

References

Merck Index 4976  
I.N. p. 527  
Borglin, J.N.; US Patent 2,217,611; October 8, 1940; assigned to Hercules Powder Co.

ISOCARBOXAZIDE

Therapeutic Function: Antidepressant
**Chemical Name:** 5-Methyl-3-isoxazolecarboxylic acid 2-benzylhydrazide

**Common Name:** -

**Structural Formula:**

![Structural Formula](image)

**Chemical Abstracts Registry No.:** 59-63-2

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**Raw Materials**

5-Methyl-3-isoxazole carboxylic acid hydrazide  
Benzaldehyde  
Lithium aluminum hydride

**Manufacturing Process**

800 g of benzaldehyde was added to a hot solution (75°C) of 7 liters of ethanol containing 720 g of 5-methyl-2-isoxazole carboxylic acid hydrazide. The solution was stirred for ten minutes at which time the product began to crystallize. On cooling at 4°C for 14 hours, the solid was filtered off under vacuum and the solid filter cake was washed twice using 250 ml of ice cold ethanol for each washing. The 1-benzylidene-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine was recrystallized from ethanol, MP 199°C to 200°C.

115 g of 1-benzylidene-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine was added portionwise over the period of an hour to 5 liters of anhydrous ether containing 18.5 g of lithium aluminum hydride. The reaction mixture was stirred for four hours and permitted to stand overnight. The excess lithium aluminum hydride was decomposed with 250 ml of ethyl acetate and 150 ml of water was added to decompose the complex. The solid was separated by filtration and the ether layer was concentrated to about 500 ml. 200 ml of benzene was added to dehydrate the solution. Concentration was continued until a solid remained. The 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine was recrystallized from methanol, MP 105°C to 106°C.

**References**

Merck Index 5003  
Kleeman and Engel p. 500
ISOCONAZOLE NITRATE

**Therapeutic Function:** Antibacterial, Antifungal

**Chemical Name:** 1-[(2,4-Dichloro-β-[(2,6-dichlorobenzyl)oxy]phenylethyl] imidazole nitrate

**Common Name:** -

**Structural Formula:**

![Structural formula of Isoconazole Nitrate]

**Chemical Abstracts Registry No.:** 24168-96-5; 27523-40-6 (Base)

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**Raw Materials**

- α-(2,4-Dichlorophenyl)imidazole-1-ethanol
- Sodium hydride
- 2,6-Dichlorotenzyl chloride
Manufacturing Process

To a stirred and refluxing solution of 40 parts of benzene and 35 parts of dimethylformamide (both solvents previously dried azeotropically) are added successively 1.6 parts of sodium hydride and 7.7 parts of \( \alpha \)-(2,4-dichlorophenyl)imidazole-1-ethanol, (cooling on ice is necessary). After the addition is complete, stirring and refluxing is continued for 30 minutes. Then there are added 7.8 parts of 2,6-dichlorobenzyl chloride and the whole is stirred at reflux for another 3 hours. The reaction mixture is poured onto water and the product 1-[2,4-dichloro-b-(2,6-dichlorobenzyloxy)phenethyl] imidazole, is extracted with benzene. The extract is washed twice with water, dried, filtered and evaporated in vacuo. The base residue is dissolved in a mixture of acetone and diisopropyl ether and to this solution is added an excess of concentrated nitric acid solution. The precipitated nitrate salt is filtered off and recrystallized from a mixture of methanol and diisopropyl ether, yielding 1-[2,4-dichloro-b-(2,6-dichlorobenzyloxy)phenethyl]imidazole nitrate; melting point 179°C.

References

Merck Index 5007  
DFU 4 (11) 814 (1979)  
Kleeman and Engel p. 500  
DOT 15 (12) 542 (1979) and 17 (9) 388 (1981)  
I.N. p. 528  
Godefroi, E.F. and Heeres, J.; US Patents 3,717,655; February 20, 1973 and 3,839,574; October 1, 1974; both assigned to Janssen Pharmaceutica NV

ISOETHARINE

Therapeutic Function: Sympathomimetic, Bronchodilator

Chemical Name: 2-Benzenediol, 4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-

Common Name: Etyrenalinum; Isoetharine

Structural Formula:
Chemical Abstracts Registry No.: 530-08-5

**Raw Materials**

- 3,4-Dibenzyl-hydroxy-butyrophenone
- Bromine
- Isopropylamine
- Palladium on carbon

**Manufacturing Process**

36 g 3,4-dibenzyl-hydroxy-butyrophenone was dissolved in 125 ml methylene chloride and 16 g bromine was added dropwise after 15 g calcium carbonate. An obtained precipitate was filtered off. The filtrate was distilled to dryness to give 1-(3,4-dibenzyloxy-phenyl)-2-bromo-butan-1-one. It was dissolved in a portion of ethanol and 15 g of isopropylamine was added. The mixture had stood for night at room temperature and thereafter ether was added. The isopropylamine hydrobromide had fallen. It was filtered off, the filtrate was shook with 200 ml of diluted hydrochloric acid. At that 4-(1-hydroxy-2-isopropylamino-butyl)-benzene-1,2-diol chlorohydrate was separated as an oil. The oil was diluted with the 5 volumes of ethanol and the calculated quantity hydrogen was passed through in a presence of palladium on coal catalyst. The catalyst was filtered off and a solvent was removed to dryness, the residue had crystallized by grinding with acetone. The obtained 4-(1-hydroxy-2-isopropylamino-butyl)-benzene-1,2-diol chlorohydrate was recrystallized from methanol. MP: 212°-213°C. Chlorohydrate may be changed into isoetharine with the calculated quantity of any base.

**References**

D.R. Patent No. 638,650; June 8, 1934; I.G.Farbenindustrie Akt.-Ges. in Frankfurt a.M.

**ISOFLUPREDONE**

**Therapeutic Function:** Glucocorticoid

**Chemical Name:** Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-, (11β)-

**Common Name:** Deltafludrocortisone, 9-Fluorprednisolone, Isoflupredone

**Chemical Abstracts Registry No.:** 338-95-4
**Structural Formula:**

![Structural Formula](image)

**Raw Materials**

- Potassium dihydrogen phosphate
- Disodium hydrogen phosphate
- *Corynebacterium simplex*
- $9\alpha$-Fluoro-4-pregnen-11\(\beta\),17\(\alpha\),21-triol-3,20-diene

**Manufacturing Process**

A 100 ml broth culture containing a 0.1% yeast extract concentration, 9.0 ml of 0.2 M KH$_2$PO$_4$ and 9.0 ml of 0.2 M Na$_2$HPO$_4$ contained in a 300 ml Erlenmeyer flask, is seeded with 1 ml of a 24-h broth culture of *Corynebacterium simplex* (A. T. C. C. 6946). The flask is incubated at 28°C for 24 h. A second 300 ml Erlenmeyer flask containing 150 mg of sterile $9\alpha$-fluoro-4-pregnen-11\(\beta\),17\(\alpha\),21-triol-3,20-diene in 5.0 ml acetone is inoculated with the 24 h culture of *Corynebacterium simplex* (A. T. C. C. 6946). The culture-containing steroid solution is incubated for 48 h at 28° to 30°C.

The product is extracted with chloroform and isolated by evaporation to dryness. Recrystallization of the residue affords $9\alpha$-fluoro-\(\delta^1,4\)-pregnadiene-11\(\beta\),17\(\alpha\),21-triol-3,20-dione as a solid.

**References**


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**ISOFLURANE**

**Therapeutic Function:** Inhalation anesthetic

**Chemical Name:** 1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether
Common Name: -

Structural Formula:

![Structural formula of Isoflurophate]

Chemical Abstracts Registry No.: 26675-46-7

Raw Materials

- 1-Chloro-2,2,2-trifluoroethyl dichloromethyl ether
- Hydrogen fluoride

Manufacturing Process

A 1-liter 3-necked stainless steel flask was fitted with a copper "Dry Ice" cold finger condenser, a stainless steel stirring shaft and gland and a copper gas inlet tube. To the flask there was then added 50 g (0.23 mol) of CF₂CHClOCHCl₂ and 1.5 g of SbCl₅ · HF gas was then slowly bubbled through the stirred mixture which was maintained at 0°C. The reaction was run until 0.35 mol of HCl was collected, as indicated by the titration of the effluent gas which was dissolved in water. Following the fluorination 26 g of material were recovered and determined to be 90% pure by vapor phase chromatography. Fractional distillation using a 30 x 0.5 cm column packed with glass helices gave the pure product, BP 48°C to 48.5°C.

References

Merck Index 5021
DOT 16 (11) 374 (1980)
I.N. p. 528
REM p. 1042

ISOFLUROPHATE

Therapeutic Function: Cholinergic (ophthalmic)
Chemical Name: Phosphorofluoridic acid bis(1-methylethyl)ester

Common Name: Fluostigmine

Structural Formula:

[Chemical Abstracts Registry No.: 55-91-4]

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Raw Materials

- Isopropanol
- Chlorine
- Phosphorus trichloride
- Sodium fluoride

Manufacturing Process

212 lb (3.54 lb-mols) of isopropanol containing less than 0.2 wt % of water was cooled with brine to -5°C in a jacketed reactor. 160 lb (1.16 lb-mols) of phosphorus trichloride was gradually added to the isopropanol with cooling and stirring during a period of 4 hours. The temperature of the reaction was not allowed to exceed 12°C and the system was maintained under slight negative pressure (about 700 mm) to remove undesirable vapors.

After completion of the addition, the mixture was stirred for ½ hour and then subjected to a pressure of 12 to 100 mm of mercury. Chlorine was then passed into the crude reaction product at a rate of 12 lb/hr, the temperature of the reaction being kept below 12°C by brine cooling. The end of the reaction was indicated by a temperature drop which occurred after a total of 122 lb of chlorine (1.72 lb-mols, 48% excess) was used.

To remove excess chlorine, hydrogen chloride and isopropyl chloride, the well-stirred mixture was subjected to a pressure of 12 to 100 mm of mercury for 2 hours. The temperature was gradually raised to 20°C during this time by passing steam into the jacket of the reactor. 10 gallons of benzene was then added and distilled off under reduced pressure, gradually raising the
temperature of the reaction mixture to 30°C. The last traces of hydrogen chloride were removed by adding an additional 10 gallons of benzene which was distilled off under reduced pressure at reactor temperatures not exceeding 50°C. The total time required for the removal of the volatile acid components of the reaction mixture was 4 hours.

The mixture was then cooled to 20°C and 19 gallons of benzene was added. This was followed by the introduction of 123.5 lb (2.80 lb-mols) of dry powdered sodium fluoride (95% pure). The mixture was stirred and heated to the refluxing temperature in a period of 1 hour and held at this temperature (95° to 98°C) for 4 hours. The product obtained was cooled and filtered to yield a filter cake which was washed with three 5-gallon portions of benzene. The filtrate and washing were then combined and distilled under reduced pressure. There was obtained 158 lb (74% yield of theory based on PCl₃) of diisopropyl fluorophosphate, BP 62°C at 9 mm and 46°C at 5 mm.

References

Merck Index 5022
Kleeman and Engel p. 501
PDR p. 1179
I.N.p. 437
REM p. 899
Hardy, E.E. and Kosolapoff, G.M.; US Patent 2,409,039; October 8, 1946; assigned to Monsanto Chemical Company

ISOMETHEPTENE

Therapeutic Function: Muscle relaxant

Chemical Name: N,1,5-Trimethyl-4-hexenylamine

Common Name: Methyl isooctenylamine

Structural Formula:

Chemical Abstracts Registry No.: 503-01-5

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**Raw Materials**

- Methyl heptenone
- Methylamine

**Manufacturing Process**

Methyl heptenone dissolved in 75% alcohol is reduced with activated aluminum in the presence of methylamine to give isometheptene.

**References**

- Merck Index 5031
- Kleeman and Engel p. 502
- PDR pp. 654,781
- I.N. p. 529
- REM p. 891
- Klavehn, W. and Wolf, A.; US Patent 2,230,753; February 4, 1941; assigned to E. Bilhuber Corporation, Germany
- Klavehn, W. and Wolf, A.; US Patent 2,230,754; February 4, 1941; assigned to E. Bilhuber Corporation, Germany

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**ISONIAZID**

**Therapeutic Function:** Antitubercular

**Chemical Name:** 4-Pyridinecarboxylic acid hydrazide

**Common Name:** Isonicotinic acid hydrazide

**Structural Formula:**

\[
\text{Chemical Abstracts Registry No.: } 54-85-3
\]

**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
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Nyrazid | Squibb | US | 1952
Niconyl | Parke Davis | US | 1952
INH | Lilly | US | 1952
Tisin | U.S.V. Pharm. | US | 1952
Pyrizidin | Warner Lambert | US | 1952
Cotinazin | Pfizer | US | 1952
Tyvid | Merrell National | US | 1952
Ditubin | Schering | US | 1952
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**1970 Isopropamide iodide**

### Raw Materials

4-Cyanopyridine  
Hydrazine hydrate

### Manufacturing Process

4 parts of 4-cyanopyridine in 12 parts of water were reacted with 4 parts of hydrazine hydrate in the presence of 0.08 part of sodium hydroxide at 100°C under reflux for 7 hours. The product, after filtration and evaporation to dryness, was crystallized from ethanol. The yield of isonicotinyl hydrazide amounted to 3.27 parts which is 62% of the theoretical.

### References

Merck Index 5032  
Kleeman and Engel p. 503  
PDR pp. 798, 830, 1237  
OCDS Vol. 1 p. 254 (1977) and 2,266 (1980)  
I.N. p. 529  
REM p. 1214  
Gasson, E.J.; US Patent 2,830,994; April 15, 1958; assigned to The Distillers Company Limited, Scotland  
Fox, H.H.; US Patent 2,596,069; May 6, 1952; assigned to Hoffmann-La Roche Inc.

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**ISOPROPAMIDE IODIDE**

**Therapeutic Function:** Spasmolytic

**Chemical Name:** γ-(Aminocarbonyl)-N-methyl-N,N-bis(1-methylethyl)-γ-phenylbenzenepropanaminium iodide
Common Name: Diisopropylaminodiphenylbutyramide methiodide

Chemical Abstracts Registry No.: 71-81-8

Raw Materials

\(\gamma\)-Diisopropylamino-\(\alpha,\alpha\)-diphenylbutyronitrile
Sulfuric acid
Methyl iodide

Manufacturing Process

\(\gamma\)-Diisopropylamino-\(\alpha,\alpha\)-diphenylbutyronitrile (60 g) was added in several portions to a mixture of sulfuric acid (150 ml) and water (15 ml) and the solution was heated 3% hours on the steam bath and then poured on ice and made basic with \(\text{NH}_4\text{OH}\). The \(\gamma\)-diisopropylamino-\(\alpha,\alpha\)-diphenylbutyramide precipitated as a solid, which was taken up in methylene chloride from an aqueous slurry. The methylene chloride was separated and dried by filtering through anhydrous \(\text{K}_2\text{CO}_3\). The solvent was removed by distillation, leaving the amide which was crystallized from Skellysolve B five times and found then to have MP 87.0° to 88.5°C.

\(\gamma\)-Diisopropylamino-\(\alpha,\alpha\)-diphenylbutyramide in propanol was refluxed 4 hours in the presence of excess methyl iodide. Upon dilution of the solution with ethyl acetate (100 ml per 50 ml isopropyl alcohol) and cooling \(\gamma\)-diisopropylamino-\(\alpha,\alpha\)-diphenylbutyramide methiodide precipitated, was collected by filtration and recrystallized (9.0 g) by dissolving in a hot mixture
of 100 ml isopropyl alcohol and 10 ml methanol and then diluting with 90 ml Skellysolve B, to give 8.3 g recrystallized product, MP 182° to 184°C.

References

Merck Index 5051
Kleeman and Engel p. 504
PDR pp. 1606, 1706, 1711, 1999
I.N. p. 531
REM p. 916
Speeter, M.E.; US Patent 2,823,233; February 11, 1956; assigned to Bristol Laboratories Inc.

ISOPROTERENOL SULFATE

Therapeutic Function: Bronchodilator

Chemical Name: 4-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-1,2-benzenediol sulfate

Common Name: Isoprenaline sulfate; Isopropylarterenol sulfate

Structural Formula:

Chemical Abstracts Registry No.: 299-95-6; 7683-59-2 (Base)

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Raw Materials

- 3,4-Dihydroxy-ω-chloroacetophenone
- Hydrogen
- Isopropylamine
- Sulfuric acid

Manufacturing Process

As described in US Patent 2,308,232, 100 g 3,4-dihydroxy-ω-chloroacetophenone, 200 cc ethyl alcohol and 200 cc of about 50% aqueous isopropylamine solution are boiled during 3 hours on the water bath with the use of a reflux condenser, whereupon neutralizing with diluted sulfuric acid is carried out and the sulfate, obtained upon cooling, from alcohol of 50% is recrystallized; its MP is 245°C.

21 g 3,4-dihydroxy-ω-isopropylaminoacetophenone sulfate are hydrogenated with 50 cc methyl alcohol and 50 cc water, 0.5 g carbon and 3 cc palladium chloride solution of 2%. After 2 hours the hydrogen absorption comes to a standstill, after the theoretical quantity of hydrogen has been absorbed. After concentrating, the isopropylaminomethyl-(3,4-dihydroxyphenyl)carbinolsulfate crystallizes out. It has a MP of 180°C after refining.

References

Merck Index 5065
Kleeman and Engel p. 503
I.N. p. 531
REM p.886
Delmar, G.S. and Macallum, E.N.; US Patent 2,715,141; August 9, 1955; assigned to Delmar Chemicals Limited, Canada
ISOSORBIDE DINITRATE

Therapeutic Function: Coronary vasodilator

Chemical Name: 1,4:3,6-Dianhydro-D-glucitol dinitrate

Common Name: Dinitrosorbide

Structural Formula:

Chemical Abstracts Registry No.: 87-33-2

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**Isothipendyl hydrochloride** 1975

**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
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Isotrate | Hauck | US | -
Laserdil | Laser | US | -
Marrolingual | Pohl-Boskamp | W. Germany | -
Maycor | Parke Davis | W. Germany | -
Metonitron | Petazon | Switz. | -
Nitorol R | Eisai | Japan | -
Nitroret | Hishiyama | Japan | -
Nitrosit | Pharmacal | Finland | -
Nitrosorbid | Lusofarmaco | Italy | -
Nitro-Tablinen | Sanorania | W. Germany | -
Nosim | Richet | Argentina | -
Risordan | Theraplix | France | -
Soniso | Lipha | UK | -
Sorbangil | Kabi Vitrum | Sweden | -
Sorbid | I.E. Kimya Evi | Turkey | -
Tinidil | Pliva | Yugoslavia | -
Vascardin | Nicholas | UK | -

**Raw Materials**

1,4:3,6-Dianhydro-D-glucitol  
Nitric acid

**Manufacturing Process**

An aqueous syrup of 1,4:3,6-dianhydro-D-glucitol is slowly added to a cooled mixture of HNO₃ and H₂SO₄. After standing a few minutes the mixture is poured into cold water and the precipitated product is collected and recrystallized from ethanol.

**References**

Merck Index 5074  
Kleeman and Engel p. 505  
PDR pp.830, 905, 928, 993, 1442, 1606, 1784, 1951, 1999  
I.N. p. 533  
REM p. 853  
Cordes, G., Munch, U. and Giesselmann, E.; US Patent 4,156,736; May 29, 1979; assigned to Sanol Schwarz-Monheim G.m.b.H. (W. Germany)

**ISOTHIPENDYL HYDROCHLORIDE**

**Therapeutic Function:** Antihistaminic

**Chemical Name:** 10-(2-Dimethylamino-2-methylethyl)-10H-pyrido[3,2-b][1,4]benzothiazine hydrochloride
Common Name: -

Structural Formula:

![Structural Formula Image]

Chemical Abstracts Registry No.: 1225-60-1 ; 482-15-5 (Base)

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Raw Materials

- Sulfur
- Sodium amide
- Hydrogen chloride
- Phenylpyridylamine
- Dimethylaminoisopropyl chloride

Manufacturing Process

85 parts of phenylpyridyl amine, 21 parts of powdered sulfur and 1.7 parts of iodine were heated to 275°C for two hours. Evolution of hydrogen sulfide began when the mixture reached a temperature of 250°C and became vigorous when it reached 275°C. Such evolution of hydrogen sulfide diminished after about one hour at 275°C. A light oil was distilled from the reaction mixture under vacuum (pressure = 2-3 mm Hg). This oil which contained phenylpyridyl amine in addition to the thiophenylpyridyl amine was then treated at boiling temperature with approximately the theoretical amount of 2-3 normal HCl until complete solution resulted with formation of the HCl salts of the amines. The solution was then treated with 1 to 2% (based upon the substance mixture) of active carbon and then filtered hot. The nitrate was then cooled to 0°C whereupon the thiophenylpyridyl amine hydrochloride crystallized out while the phenylpyridyl amine hydrochloride remained in solution. The thiophenylpyridyl amine hydrochloride was filtered off and suspended in water and the pH adjusted with half concentrated ammonia to 8. The thiophenylpyridyl amine set free was filtered off and dried. It was in the form of gold yellow needles and had a melting point of 114°C to 115°C.
40 parts of thiophenylpyridyl amine were dissolved in 200 parts of water free toluene. After the addition of 16 parts of soda amide, the mixture was refluxed for 1% hours. Thereafter, 28 parts of dimethylaminoisopropyl chloride in 30 parts of water free toluene were dropped in and the temperature maintained at 20°C to 25°C for 30 minutes. Thereafter, the mixture was heated at 60°C for 30 minutes and subsequently refluxed for 20 minutes. Water and hydrochloride acid were then added to the reaction mixture and this mixture rendered alkaline with NaOH and then the alkalized mixture shaken out with ether. The dimethylaminoisopropyl-N9-thiophenylpyridyl amine base thus obtained was vacuum distilled. It was then converted to hydrochloride salt. The monohydrochloride salt is almost white in color and melts at 213°C to 216°C. The yield was almost 100% of the theoretical.

References

Merck Index 5077
Kleeman and Engel p. 505
OCDS Vol. 1 p.430 (1977)
I.N.p. 534
Schuler, W.A. and Klebe, H.; US Patent 2,974,139; March 7, 1961; assigned to Degussa (W. Germany)

**ISOTRETINOIN**

**Therapeutic Function:** Antiacne, Keratolytic

**Chemical Name:** Retinoic acid, 13-cis-

**Common Name:** cis-Retinoic acid; Isotretinoin

**Structural Formula:**

![Chemical Structure](image)

**Chemical Abstracts Registry No.:** 4759-48-2

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**Raw Materials**

- Butyl lithium
- Diisopropylamine
- Methyl 3,3-dimethyl acrylate
- \(\beta\)-Ionylidene acetaldehyde

**Manufacturing Process**

Under an atmosphere of nitrogen, a solution of n-butyl lithium in hexane (321 ml, 15%) was added to a solution of diisopropylamine (48.6 g, 0.48 mole) in tetrahydrofuran (1000 ml) at -30°C and the mixture was stirred for one hour. The reaction mixture was then cooled to -72°C and methyl 3,3-dimethyl acrylate (55 g, 0.48 mole) was added to it. Stirring was continued at -65° to -75°C for 30 min. To the resulting mixture, a solution of \(\beta\)-ionylidene acetaldehyde (100 g, 0.458 mole, 9-trans content: 80%) was added and the reaction mixture was stirred at -65° to -75°C for 1 h. The reaction mixture was then warmed to 40°C and stirred at this temperature for 3 h. Solvent was removed under vacuum and the reaction mixture was diluted with water (700 ml) and methanol (300 ml). Activated charcoal (4 g) was then added and the mixture was refluxed for 30 min. The heterogeneous mixture was filtered through hyflo and the hyflo bed was washed with methanol (300 ml) and water (150 ml). The aqueous methanolic layer was then extracted with hexanes (2 x 500 ml) and acidified with 10% sulfuric acid to pH 2.80.5. The desired product was then extracted with dichloromethane (2 x 500 ml). The combined dichloromethane layer was washed with water (2 x 300 ml) and concentrated in vacuo to afford the desired isotretinoin. Crystallization from methanol (200 ml) afforded isotretinoin (44 g) in greater than 99% HPLC purity.

**References**


**ISOXICAM**

**Therapeutic Function:** Antiinflammatory

**Chemical Name:** 4-Hydroxy-3-(5-methyl-3-isoxazolocarbamyl)-2-methyl-2H-1,2-benzothiazine 1,1-dioxide

**Common Name:** -
Structural Formula:

![Structural Formula Image]

Chemical Abstracts Registry No.: 34552-84-6

Raw Materials

- 3-Carbethoxy-4-hydroxy-2-methyl-2H-1,2-benzothiazine-1,1-dioxide
- 3-Amino-5-methyl-isoxazole

Manufacturing Process

A mixture of 40.5 g (0.15 mol) of 3-carbethoxy-4-hydroxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide, 20.6 g (0.21 mol) of 3-amino-5-methylisoxazole, and 2,500 ml of xylene was refluxed for 24 hours in a Soxhlet apparatus, the thimble of which contained 60 g of Linde type 4A molecular sieve. The mixture was cooled to 25°C and the resulting crystalline precipitate was collected and washed with ether to give 44 g of crude product. Recrystallization from 1,600 ml of 1,4-dioxan gave 34.7 g of material, MP 265°C to 271°C dec.

References

Merck Index 5085
DFU 1 (3) 123 (1976)
DOT 19 (2) 119 (1983) and 19 (7) 414 (1983)
I.N. p. 534

ISOXSUPRINE HYDROCHLORIDE

Therapeutic Function: Vasodilator

Chemical Name: 4-Hydroxy-α-[1-[(1-methyl-2-phenoxyethyl)amido]ethyl] benzenemethanol hydrochloride
1980  Isoxsuprine hydrochloride

Common Name: -

Structural Formula:

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Chemical Abstracts Registry No.: 579-56-6; 395-28-8 (Base)

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Raw Materials

- 1-Phenoxy-2-aminopropane
- 1-(4’-Benzyloxyphenyl)-2-bromopropanone-1
- Hydrogen

Manufacturing Process

To a solution of 30.7 g (0.203 mol) of 1-phenoxy-2-aminopropane in 150 ml of ethanol there was added 31.9 g (0.100 mol) of 1-(4’-benzyloxyphenyl)-2-bromopropanone-1. The mixture was heated to boiling temperature and the solution was then refluxed in a reflux condenser for 3 hours. Most of the ethanol was then distilled off in vacuo, Then to the residue there was added
about 150 ml of diethyl ether. The hydrogen bromide salt of 1-phenoxy-2-aminopropane was filtered off and washed with diethyl ether.

The collected ethereal filtrates were acidified with 50 ml of 4 N hydrochloric acid and this solution was stirred vigorously. The hydrochloride of 1-(4'-benzyl-oxyphenyl)-2-(1'-methyl-2-phenoxy-ethylamino)propanone-1 precipitated out, was filtered off, washed with water and then with diethyl ether. Then this substance was dried in vacuo. The yield was 37.7 g, i.e., 89% of the theoretically possible yield, calculated on 1-(4'-benzyl-oxyphenyl)-2-bromine propanone-1. This substance had a light yellow color and melted at 197 to 198°C, while decomposing.

Then 21.89 g of the hydrochloride salt was dissolved in 600 ml of 80% aqueous ethanol. With the addition of a palladium carbon catalyst, this solution was hydrogenated at room temperature under a hydrogen pressure of about 1.1 atmospheres. After 2 mols hydrogen had been absorbed, the catalyst was filtered off and the filtrate was evaporated in vacuo until crystallization occurred. Then the crystals were dissolved by heating in the smallest possible quantity of water and after cooling, the crystallized substance was filtered off, washed with water and dried in vacuo. The yield was 6.80 g, i.e., 39% of the theoretically possible yield. The resultant product recrystallized from water melted at 203° to 204°C.

References
Merck Index 5086
Kleeman and Engel p. 506
PDR pp. 830, 993, 1129, 1569, 1606, 1999
OCDS Vol. 1 p. 69 (1977)
I.N. p. 534
REM p. 892
Moed, H.D.; US Patent 3)256,836; October 2, 1962; assigned to North American Philips Company

**ITRACONAZOLE**

**Therapeutic Function:** Antifungal

**Chemical Name:** 3H-1,2,4-Triazol-3-one, 4-(4-(4-(4-(2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-1-piperazinyl)phenyl)-2,4-dihydro-2-(1-methylpropyl)-

**Common Name:** Itraconazole

**Chemical Abstracts Registry No.:** 84625-61-6
Structural Formula:

![Structural Formula Image]

**Trade Name** | **Manufacturer** | **Country** | **Year Introduced**
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Canadiol | Esteve | - | -
Candidral | Glenmark Pharmaceuticals Ltd. | India | -
Funit | Nobel | - | -
Itaspor | Intas Pharmaceuticals Pvt. Ltd. | India | -
Itraconazole | Janssen Pharmaceutica Inc. | USA | -
Itraconazole | Chemo Iberica | Spain | -
Kanazol | Slaviaimed | Yugoslavia | -
Micoral | Sintyal | - | -
Orungal | Janssen Pharmaceutica N.V. | Belgium | -
Sporacid | Dexa Medica | - | -
Sporanox | Farmasa/Neo Quimica | - | -
Sporanox | Janssen Pharmaceutica Inc. | Belgium | -
Sporanox | Ortho Biotech. Inc. | USA | -
Sporanox | Johnson and Johnson | India | -
Sporex | Toprak | - | -

**Raw Materials**

- Hydrogen
- Hydrobromic acid
- Sodium hydride
- 1-(4-Methoxyphenyl)piperazine dihydrochloride
- cis-[2-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]methanesulfonate
- 4-Methyl-2-pentanone
- 1-Chloro-4-nitrobenzene
- Potassium carbonate
- 2,4-dihydro-2-(methylpropyl)-3H-1,2,4-triazol-3-one

**Manufacturing Process**

Synthesis of cis-4-\{-4-[4-\{-4-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl\}-1-piperazinyl]phenyl\}-2,4-dihydro-2-(methylpropyl)-3H-1,2,4-triazol-3-one is showed by the same procedure as for cis-4-\{-4-[4-\{-4-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl\}-1-piperazinyl]phenyl\}-2,4-
A mixture of 13.4 parts of 1-(4-methoxyphenyl)piperazine dihydrochloride, 7.9 parts of 1-chloro-4-nitrobenzene, 10 parts of potassium carbonate and 90 parts of N,N-dimethylformamide is stirred and refluxed overnight. The reaction mixture is diluted with water and the product is extracted twice with trichloromethane. The residue is triturated in 4-methyl-2-pentanone. The product is filtered off and crystallized from 1,4-dioxane, yielding 10.5 parts (67%) of 1-(4-methoxyphenyl)-4-(4-nitrophenyl)piperazine; melting point 195.1°C.

A mixture of 12 parts of 1-(4-methoxyphenyl)-4-(4-nitrophenyl)piperazine, 200 parts of methanol and 225 parts of tetrahydrofuran is hydrogenated at normal pressure and at 20°C with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and washed with N,N-dimethylacetamide. Product is filtered off and crystallized from 1-butanol, yielding 8 parts (74%) of 4-[4-(4-methoxyphenyl)-1-piperazinyl]benzenamine; melting point 191.8°C.

A mixture of 30 parts of 4-[4-(4-methoxyphenyl)-1-piperazinyl]benzenamine and 300 parts of a hydrobromic acid solution 48% in water is stirred and refluxed for 10 days. The reaction mixture is evaporated and the residue is alkalized with sodium hydroxide. The mixture is filtered and the filtrate is acidified with acetic acid. The precipitated product is filtered off and crystallized from 1,4-dioxane, yielding 12 parts (44%) of 2,4-dihydro-4-{4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl}-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one.

To a stirred solution of 2,4-dihydro-4-{4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl}-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one in 100 parts of dimethyl sulfoxide are added 0.3 parts of sodium hydride dispersion 78% and the whole is stirred at 50°C till foaming has ceased. Then there are added 3.7 parts of cis-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]methanesulfonate and stirring is continued for 3 hours at 100°C. The reaction mixture is cooled and poured onto water. The product is extracted with dichloromethane. The extracts are washed with a diluted sodium hydroxide solution and filtered. The residue is crystallized from 1-butanol. The product yield 4.3 parts (75%) of cis-4-{4-[4-{4-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl}-1-piperazinyl]phenyl}-2,4-dihydro-2-(methylpropyl)-3H-1,2,4-triazol-3-one.

References
Heeres, J., Backx, L.J.J.; US Patent No. 4,267,179; May 12, 1981; Assigned to Janssen Pharmaceutica, N.V., Beerse, Belgium

IVERMECTIN

Therapeutic Function: Antiprotozoal
Chemical Name: A mixture of Ivermectin component B₁₈ and Ivermectin component B₁₉

Common Name: Hyvermectin; Ivermectin

Structural Formula:

![Chemical Structure Diagram]

Chemical Abstracts Registry No.: 70288-86-7; 74564-75-3

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</tbody>
</table>
Avermectin is produced by biotechnological methods with the aid of Streptomyces avermitilis.

Preparation of Catalyst I

Rhodium trichloride trihydrate (1.00 g, 3.80 mmol) was dissolved in water (5.0 ml) with heating (70°C). A solution of triphenylphosphine (1.95 g, 7.43 mmol) in acetone (25.0 ml) was then added under a nitrogen atmosphere in the course of 20 min. After 10 min hydrazine hydrate (1.90 ml; 39.09 mmol) was added with stirring and the mixture was heated at reflux temperature for 3 hours, then kept at 45°C for a further 1 hour. The crystalline solid was filtered off under nitrogen and washed with a little acetone and then with diethyl ether. 1.05 g of an orange-coloured solid were obtained.

Hydrogenation with catalyst I

The catalyst (10 mg) was dissolved in toluene (25 ml) and added under argon to the solution of a mixture (1.1 g) of avermectin B$_{1a}$ (96%) and avermectin B$_{1b}$ (4%) and of 100 mg of triphenylphosphine in toluene (25 ml) in a stainless steel autoclave. This starting material was then hydrogenated at 88°C under a hydrogen pressure of 20 bar with stirring of the solution. After 10 hours, HPLC analysis revealed a content of 86% dihydro-avermectin B$_{1a}$ and of 4 % dihydroavermectin B$_{1b}$, and also of 3% tetrahydroavermectin B$_{1a}$.

Preparation of Catalyst II

Under an atmosphere of argon, a mixture of 7.5 mg of rhodium trichloride, 30.0 mg of tris-(hexylphenyl)-phosphine, 3 ml of acetone and 15 ml of hydrazine hydrate is heated with stirring and reflux cooling for 4 hours.

Hydrogenation with catalyst II
The catalyst is added to a solution of 4.3 g of avermectin (B$_{1a}$ and B$_{1b}$ mixture) in 25 ml of a mixture of acetone and cyclohexane in a ratio of 2:1. After addition of 51.4 mg of tris-(mexylphenyl)phosphine, the hydrogenation is carried out in a steel autoclave at a hydrogen pressure 5 bar and at 88°C. After a hydrogenation time of 4 hours, 8.9% of starting material, 89.9% of ivermectin (B$_{1a}$ and B$_{1b}$ mixture), tetrahydroavermectin content <0.1% was obtained (according to HPLC analysis).

Removing of the catalyst system

The crude product after distillative removal of the solvent mixture, dissolved in a mixture of 35 ml of methanol and 20 ml of water and this solution is extracted with 25 ml of cyclohexane in a separating funnel. The phases are separated and concentrated under reduced pressure. The extraction is repeated twice in the same manner.

Result:

The crude product of the hydrogenation

690 ppm of Rh

The resulting product contains

<table>
<thead>
<tr>
<th>Extraction</th>
<th>Rh concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st extraction</td>
<td>39 ppm of Rh</td>
</tr>
<tr>
<td>2nd extraction</td>
<td>29 ppm of Rh</td>
</tr>
<tr>
<td>3rd extraction</td>
<td>22 ppm of Rh</td>
</tr>
</tbody>
</table>

References

Arlt D., Bonse G., Reisewitz F.; US Patent No. 5,656,748; August 12, 1997; Assigned: Bayer AG, Leverkusen, Germany
Arlt D., Bonse G., Reisewitz F.; US Patent No. 6,072,052; June 6, 2000; Assigned: Bayer AG, Leverkusen, Germany