Improved process for preparing L-phenylephrine hydrochloride on an industrial scale

ABSTRACT

The present invention relates to an improved process for preparing L-phenylephrine hydrochloride on an industrial scale

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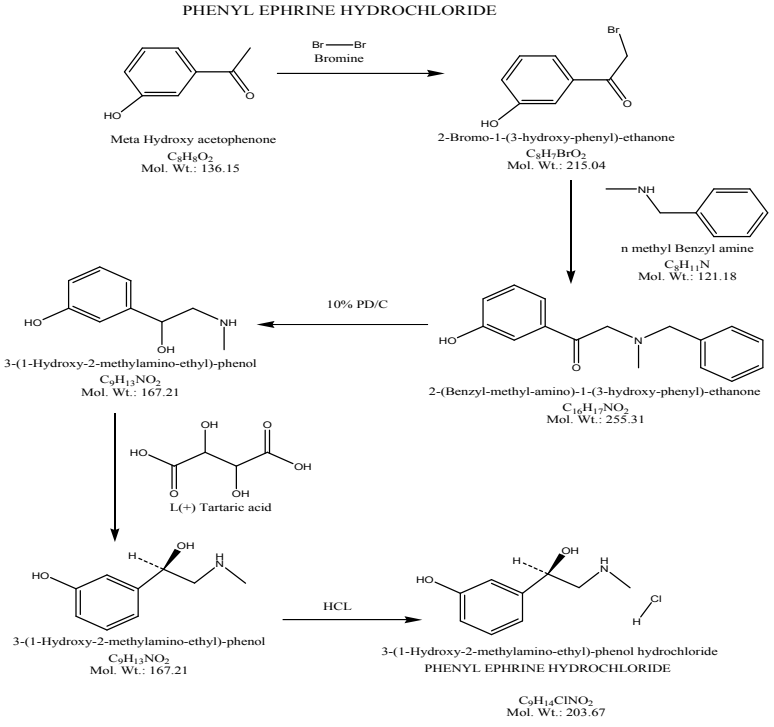
INTRODUCTION

Phenylephrine hydrochloride is an oral sympathomimetic amine that acts as a decongestant to respiratory tract mucous membranes. While its vasoconstrictor action is similar to that of ephedrine, phenylephrine has less pressor effect in normotensive adults. Serum half-life for phenylephrine is 6 to 8 hours. Acidic urine is associated with faster elimination of the drug. About one-half of the administered dose is excreted in the urine.

Meta hydroxyl acetophenone is reacted with bromine in ethyl acetate to get the bromo compound which is reacted with N-methyl benzyl amine to obtain 2-(benzyl methyl amino) - 1-(3-hydroxy phenyl) ethanone.
2-(benzyl methyl amino) - 1-(3-hydroxy phenyl) ethanone.is hydrogenated under high pressure using palladium carbon catalyst to get DL- phenylephrine base.
DL- phenylephrine base is reacted with L- tartaric acid to isolate L-phenylephrine base.
L-phenylephrine base is converted to the hydrochloride salt by treatment with IPA – HCl.



Ephedrine exhibits optical isomerism and has two chiral centre's, giving rise to four stereoisomers. By convention the enantiomers with opposite stereochemistry around the chiral centres (1R, 2S and 1S, 2R) are designated ephedrine, while pseudoephedrine has same stereochemistry around the chiral carbons (1R, 2R and 1S, 2S).

STAGE-1:

Preparation of 2-(Benzoyl methyl Amino)-1-(3-Hydroxy phenyl) ethanone from Meta hydroxyl acetophenone in presence of bromine & n-Methyl benzyl amine.

Arrange a 4 necked RBF with a mechanical stirrer, powder funnel with condenser, thermometer pocket & thermometer. Charge 3-Hydroxy acetophenone in ethyl acetate (525ml) in RBF at 30-35°C.Start chilling and add Aluminum chloride .Meanwhile charge ethyl acetate in conical flask with chilling and add bromine, mix well(Slight exothermic reaction).Start the addition of bromine solution. After the addition of 70% bromine solution reaction mass becomes a clear solution

After the addition, maintain the reaction mass for 2 hrs.After the maintenance, raise the temperature to 10°C.Then charge toluene (1285ml).Charge (1200ml) water to the reaction mass. Keep it stirring for 30 mins & separate the layers. Wash the aqueous layer with (345ml) toluene. Both the toluene layers are collected. Wash the toluene layer with (900ml) 2% sodium bicarbonate solution. Wash the toluene layer with (600ml) D.M. water. Repeat the step twice. Collect the toluene layer in conical flask & add sodium sulphate

Take the toluene layer in RBF & chill to 0°C.Start the addition of n- Methyl Benzyl amine & maintain the reaction mass for 2 hrs at 0-5°C.Filter the reaction mass & wash with toluene(200ml)

Wet cake: 285gm

Collect the mother liquor in RBF & start the addition of IPA-HCl solution

Heat the reaction mass to 50-55°C & maintain for 1 hr

Cool the reaction mass to RT

Then chill the reaction mass to 0-2°C & maintain for 1 hr

Filter the product & wash with chilled (200ml) toluene & (200ml) chilled ethyl acetate

RESULTS:

1) Wet weight of the compound: 900gm
2) Dry weight of the compound: 507gm
3) Melting point: 180-189°C

STAGE-2: Preparation of 3-(1-hydroxy-2-methyl amino ethyl) phenol.

1) Stage-1 product: 1000gm
2) Methanol: 6 lit
3) Palladium 10% : 125gm
4) Carbon: 10gm
5) Liquid Ammonia: 1080ml
6) D.M.water: 1700ml

Arrange a 4 necked RBF with a mechanical stirrer, powder funnel with condenser, thermometer pocket & thermometer. Charge 1kg stage-1 product in RBF and add 5 lit fresh methanol and start heating. Reflux the reaction mass. Add 10gm carbon & stir for 30 min at reflux temperature

Filter the reaction mass by hyflo bed & wash with 1 lit methanol. Collect the mother liquor

Further hydrogenation step is carried out .The hydrogenated mother liquor is then distilled out under vacuum. After completion of distillation, the reaction mass was cooled to 40°C, stir for 1 hr

Add 1500ml D.M water & cool to RT, stir for 1 hr .Start the addition of liquid ammonia & maintain the pH at 9.5-9.7.After the addition, add seeding material (2.0gm) & maintain for 6 hrs at RT

Then start chilling the reaction mass & maintenance is started.

Filter the reaction mass & wash with (200ml) chilled D.M. water.

1) Wet weight of the compound: 610gm
2) Dry weight of the compound: 350gm

STAGE-3A: Preparation of 3-(1-Hydroxy -2- Methyl Amino Ethyl) Phenol.

1) Stage-2product: 300gm
2) Isopropyl Alcohol (IPA): 750ml
3) L(+) Tartaric acid : 300gm
4) Liquid Ammonia: 500ml
5) D.M. water:1350ml

Arrange a 4 necked RBF with a mechanical stirrer, powder funnel with condenser thermometer pocket & thermometer. Charge IPA in RBF under stirring add (300gm) stage—2 product .Then charge L+ tartaric acid & heat up to 55-60°C.Then maintain the reaction mass for 1 hr .After the maintenance, cool the reaction mass to RT. Charge the seeding material & cool the mixture to RT .Maintain the mixture at RT for 12hrs.Filter the reaction mass & wash with (100ml) IPA 15%.Collect the mother liquor & adjust the pH to 9.5-9.7 with Liquid ammonia, stir for 30 mins .Cool the mixture to 0-5°C, stir for 3 hrs at 0-5°C.Filter the reaction mass & wash with IPA (150ml).Then charge D.M. water (750ml)

Heat the reaction mass to 65-70°C.Stir the mixture for 1 hr

Cool the reaction mass to RT. Cool the mixture to 0°C, stir for 2 hrs at 0-5°C

Filter the product & wash with chilled D.M. water (600ml)

Dry the wet cake at 50-55°C

RESULTS:

1) Wet weight of the compound: 158gm
2) Dry weight of the compound: 86gm
3) Melting point: 168-172°C
4) Appearance: Light brown coloured powder
5) % yield: 0.285%

STAGE-3B:

AIM: Recovery of 3-(1-Hydroxy -2- Methyl Amino Ethyl) Phenol from salt.

REQUIREMENTS:

1) Stage-3 A product: 276gm
2) Carbon : 10gm
3) Liquid Ammonia: 300ml
4) D.M. water:600ml

Arrange a 4 necked RBF with a mechanical stirrer, powder funnel with condenser, thermometer pocket & thermometer

Charge (600ml) D.M. water in RBF under stirring add (276gm) stage-3A product

Heat the reaction mass to 60°C & then charge (10gm) carbon. Maintain the reaction mass for 1 hr at 60-65°C.Filter the reaction mass under hyflo bed & collect the mother liquor. Adjust the pH to 9.0-9.5 with liquid Ammonia. Maintain it for 30 mins at 60°C.Cool the mixture to RT. Filter and wash with (200ml) D.M. water.(Repeat the step twice)Charge (438ml) Acetic Anhydride in RBF & add (76gm) salt obtained above slowly.(88gm) Sulphuric acid is added slowly in 2 hrs .Maintain for 1 hr at RT .Heat the mixture to 100-105°C.Maintainat 100-105°C for 1 hr .Cool the mixture to 80°C.Completely distill out Acetic Anhydride under vacuum at 80°C.Cool to 40°C.Slowly add (135ml) D.M water .Heat the reaction mass to 85°C.Maintain the mixture for 3 hrs at 80-85°C.Then cool to 40°C.Slowly add Liquid Ammonia (21ml) .Distill out D.M. water completely under vacuum. Charge (279ml) D.M.water slowly. Heat to 85°C.Maintain the mixture for 3 hrs at 80-85°C.Cool the mixture to 40°C.Start the addition of liquid ammonia (39ml) .Distill out water completely under vacuum. Cool the mixture to 40°C.Charge (555ml) D.M water slowly. Heat the reaction mass to 85°C.Maintain the mixture for 3 hrs at 80-85°C.Cool the mixture to 40°C.Adjust the pH to 9-9.5 with liquid Ammonia. Stir for 30 mins. Filter and wash with (300ml) D.M water. Charge (250ml) IPA (10% moisture content) into an RBF and charge the above dried material. Heat the mixture to reflux temperature and maintain at this temperature for 1 hr. Cool the mixture to RT .Wash the product with (35ml) IPA (10% moisture content)

Dry the product

RESULTS:

1) Wet weight of the compound: 65gm
2) Dry weight of the compound: 50.5gm

Melting point: 169°C -172°C

STAGE-4:

Preparation of 3-(1-Hydroxy -2- Methyl Amino Ethyl) Phenol Hydrochloride i.e., Phenylephrine hydrochloride.

REQUIREMENTS:

1) Stage-3B product: 61gm
2) Methanol: 900ml
3) Carbon: 12gm
4) Acetone: 150ml
5) IPA -HCl: 140ml

Arrange a 4 necked RBF with a mechanical stirrer, powder funnel with condenser, thermometer pocket & thermometer. Charge (900ml) methanol in RBF under stirring add (61gm) stage-3B product .Then charge charcoal & stir for 30 mins .Filter the reaction mass through hyflow bed & wash with (50ml) methanol & collect the mother liquor. Again add charcoal (5gm), stir for 30 mins under stirring.Filter the reaction mass through hyflo bed & wash with (100ml) methanol & collect the mother liquor.Charge IPA HCl under stirring.Complete the addition.Stir the reaction mass for 30 mins.Distill out methanol under vacuum.Add (150ml) Acetone & stir for 1 hr at RT .Chill the reaction mass to 10-15°C & maintain for 1 hr.Filter the product & wash with (50ml) Acetone

3)

RESULTS:

1) Wet weight of the compound: 69gm
2) Dry weight of the compound: 65gm
3) Melting point: 143-145°C
4) Optical rotation : -43.79
5) % yield: 1.06%
6) Purity by HPLC: 99.45%
7) Appearance: Almost white powder

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