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A PROCESS FOR THE PREPARATION OF OPTICALLY PURE D(+) BROMPHENIRAMINE AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

Yogesh A. Tawar aJaipur National University-Jaipur, Rajasthan

Raju M. Patil The Institute of Science, Mumbai

Rama S. Lokhande Jaipur National University-Jaipur

Dilip H. Ner Supriya Lifescience Limited

ABSTRACT

A new synthesis for the preparation of optically pure D(+)-3-(4-bromophenyl)-N,N-dimethyl-3-pyridin-2-yl-propan-1-amine (Brompheniramine) and its pharmaceutically acceptable salts by efficient and cost-effective process for obtaining highly optically pure Dexbrompheniramine in high yield by the resolution of a racemic mixture of 3-(4-bromophenyl)-N,N-dimethyl-3-pyridin-2-yl-propan-1-amine (brompheniramine base) with a (+)4-nitro tartranilic acid(PNTA) as a resolving agent in the presence of a alcoholic solvent system with the simultaneous recovery of the (+)4-nitro tartranilic acid(PNTA) as well as recovery of undesired (Levo)-isomer of brompheniramine and traces (Dextro)-isomer and racemization thereof to racemic mixture of brompheniramine for use in the process of the invention so as to minimize wastage of the reactants.

KEYWORDS

INTRODUCTION

Interest in the synthesis of pure enantiomers has gained new impetus because of the increasing awareness of the importance of optical purity in the context of biological activity. Brompheniramine is commonly available as a racemate. Dextro-isomer of Brompheniramine is reported1 to be more potent, approximately 80 times more potent, than its Levo-isomer. Brompheniramine commonly marketed as its salt Brompheniramine maleate, is an antihistamine drug of the propylamine[2] class. Brompheniramine is part of a series of antihistamines including pheniramine and its halogenated derivatives and others including fluorpheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine and iodopheniramine.

Brompheniramine has antidepressant properties, Brompheniramine is a analog of chlorpheniramine2. The only difference is that the chlorine atom in the benzene ring is replaced with a bromine atom. It is also synthesized in an analogous manner. Brompheniramine works by acting as an antagonist of histamine H1receptors. It also functions as a moderately effective anticholinergic agent[3], and is likely an antimuscarinic agent similar to other common antihistamines such as diphenhydramine. Brompheniramine is metabolised by cytochrome P450s. Brompheniramine's effects on the cholinergic system4 may include side-effects such as drowsiness, sedation, dry mouth, dry throat, blurred vision, and increased heart rate. It is listed as one of the drugs of highest anticholinergic activity in a study of anticholinergenic burden, including long-term cognitive impairment.

Dexbrompheniramine is an antihistamine with anticholinergic properties used to treat allergic conditions such as hay fever or urticaria[4]. It is the pharmacologically active dextrorotatory isomer of brompheniramine. The halogenated alkylamine antihistamines all exhibit optical isomerism and brompheniramine products contain racemic brompheniramine maleate whereas dexbrompheniramine is the dextrorotary (right-handed) stereoisomer. It was formerly marketed in combination with pseudoephedrine under the name Drixoral[5] in the US and Canada. Dexbrompheniramine is a first generation antihistamine that reduces the effects of natural chemical histamine in the body; sneezing, itching, watery eyes, and runny nose.

U.S. Patent Specification No. 3,061,517 describes a process for the separation of the d-isomers of phenyl-(2-pyridyl)-alkyl substituted tertiary amines and certain halogen-substituted derivatives thereof from a racemic mixture of same. However, the resolving agent, d-phenylsuccinic acid[6], used in this process is difficult to prepare and therefore expensive. The reaction must also be carried out in an organic solvent. Furthermore, successive purification steps by recrystallisation are required with consequent low yields of the end products.

Ir. Short-Term Pat. Appl., 9500206, 01 Nov 1995 describes a process by using sodium L-tosyl-aspartate and sodium D-tosyl-aspartate used1 in this process is also difficult to prepare and expensive. The process results into high enantiomeric excess but low overall yield and time consuming. This process also requires additional crystallization thereby lowering the overall yield. The resolving agent L-tosyl-aspartate and sodium D-tosyl-aspartate is not recovered and reused. The undesired (L)-isomer Brompheniramine is also not converted into desired (R)-isomer.

An object of the invention is to provide an efficient and cost-effective process for the preparation of highly optically pure Dexbrompheniramine in high yield by the resolution of a racemic mixture of brompheniramine precursor with a (+)4-nitro tartranilic acid(PNTA) as a resolving agent[6,7] in the presence of a alcoholic solvent system consist of mainly methanol with the simultaneous recovery of the (+)4-nitro tartranilic acid and simultaneous recovery of undesired (Levo)-isomer of brompheniramine and traces (Dextro)-isomer and racemization thereof to racemic mixture of brompheniramine for use[8-10] in the process of the invention so as to minimize wastage of the reactants.

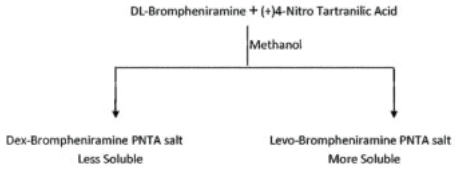
We have tried various resoluting agents like L-Tartaric acid, L-Mandelic acid, D-Mandelic acid, Camphor-10-sulphonic acid, L-Lactic acid, Di-p-toluoyl-L-tartaric acid, Dibenzoyl-L-Tartaric acid in numerous solvents and found that only 4-nitro tartranilic acid was useful as it gives better separation and both 4-nitro tartranilic acid and another isomer can be recycled and reused during the process.

EXPERIMENTAL

(+)4-nitro tartranilic acid(PNTA) is reacted with dl-brompheniramine base in alcoholic solvent mainly methanol and refluxed for few hours to get PNTA salt of brompheniramine (Compund A). The salt is filtered off at 58°C-60°C. Compund A is then hydrolysed with concentrated Hydrochloric acid under stirring for 4 hrs at room temperature. The product is filtered to get PNTA. The recovered PNTA is recycled for further use. The filtrate is basified

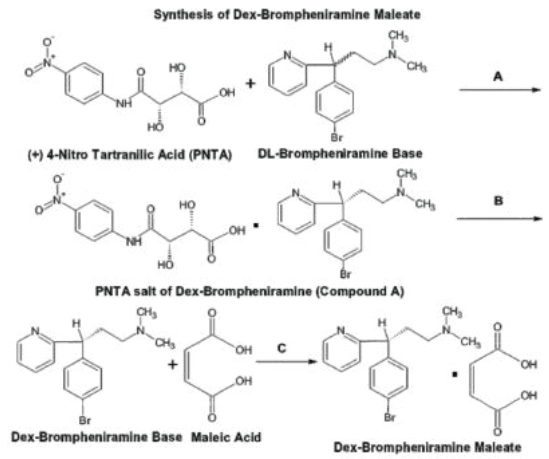
with caustic lye to pH 9-9.5 and the dexbrompheniramine base is extracted with o-Xylene. The o-Xylene layer is charcoalised and then dexbrompheniramine base is extracted in water by giving formic acid treatment. Then the aqueous layer is basified with caustic lye to pH 9-9.5 and then extracted by ethyl acetate. The ethyl acetate layer is charcoalised. Distill out ethyl acetate under vacuum below 50°C. Weigh the dexbrompheniramine base.

Charge ethyl acetate and maleic acid in RBF, heat the content to 50-55°C, the solution becomes clear. To this add solution of dexbrompheniramine base in ethyl acetate. Maintain temperature of reaction mass to 40-45°C for 2 hrs. Cool the reaction mass to room temperature and further chill 5-10°C and maintain for 1.5 hrs. Filter the solid and wash it with chilled ethyl acetate. The filtered wet cake is leached with ethyl acetate at 0°C for 1hr and filtered to get pure Dex-brompheniramine maleate. Unload the solid and dry at 60-65°C.

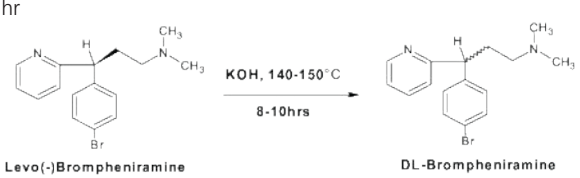


Take methanol filtrate from resolution and distill out under vacuum below 50°C to get of PNTA salt of Levo-Brompheniramine, treated with Hydrochloric acid in DM Water under stirring for 4 hrs at room temperature. The precipitated solid is filtered to get PNTA. The recovered PNTA is recycled for further use. The aqueous filtrate is basified by 50% caustic solution at room temperature. The basified aqueous is extracted by o-xylene. Distill out o-xylene under vacuum and degass to get Levo-Brompheniramine base. To Levo-Brompheniramine base add potassium hydroxide flakes and heat to 140-150°C for 8-10 hrs. Cool reaction mass to room temperature add water and o-xylene, stir, settle and separate o-xylene layer and keep it aside. Take aqueous layer and extract with o-xylene. Combine both the o-xylene layers and wash with water 2-3 times. Distill out o-xylene completely under vacuum to get crude Brompheniramine base. High vacuum distillation(HVD) of crude Brompheniramine base is done to get pure Brompheniramine base.

REACTION SCHEME:-



(A)-Methanol, 60-65°C, 4 hrs, 58-60°C
(B)-DM Water, conc.HCl, RT, 4hrs, 50% NaOH, pH 9-9.5, o-Xylene, 20% Formic acid, Ethyl acetate, RT
(C)-Ethyl Acetate, 50-55°C, 40-45°C, 2hrs, RT, 10-15°C, 0-5°C, 1hr



1) Resolution of DL-Brompheniramine Base:
4-Nitrotartranilic acid (91 g, 0.337 moles) is dissolved in 1183 ml methanol (13 parts of PNTA) under stirring at 60-65°C to get a clear solution. 3-(4-bromophenyl)-N,N-dimethyl-3-pyridin-2-yl-propan-1-amine (Brompheniramine base) (50g, 0.157moles) is slowly added under stirring at 60-65°C and refluxed for 4-5 hrs. The reaction mass is allowed to cool to 58-60°C and the solid precipitated is filtered to get 62 g PNTA salt of Dex-Brompheniramine. (Yield=82.27%, M.P.=179-181°C, SOR=+80 c=5% DMF).

2) Breaking of PNTA salt of Dex-Brompheniramine:
55g of PNTA salt of D-Brompheniramine is treated with 55ml concentrated Hydrochloric acid in 165ml of Demineralised water under stirring for 4 hrs at room temperature. The precipitated solid is filtered to get PNTA. The recovered PNTA is recycled for further use. The filtrate aqueous is basified by 50% caustic solution till pH becomes 9.0-9.5 at room temperature. The basified aqueous is extracted by o-xylene (100ml x 2). The o-xylene layer is charcolised, washed with 20ml o-xylene and treated with 20% v/v formic acid solution (30ml x 2) to extract the product in aqueous layer. The aqueous layer is again basified with 50% caustic solution till pH 9.0-9.5 and extracted in ethyl acetate (91ml x 2). The ethyl acetate layer is washed with 70ml of DM water. The ethyl acetate layer is charcolised washed with 20ml ethyl acetate. The ethyl acetate layer is distilled out under vacuum below 55-60°C, degassed well to get 16g oil of D-Brompheniramine base. (Yield= 78.32%, SOR=+75°; c=10% Toluene).

3) Preparation of Dex-Brompheniramine Maleate
Maleic acid (5g, 0.043) is dissolved in 96ml ethyl acetate under stirring and heated to 50-55°C, cooled to 40-45°C and charged Dex-brompheniramine base (16g, 0.05 moles). Stir for 2 hrs at 40-45°C. Check pH (5.0 to 6.0), cooled to room temperature, further chilled to 10-15°C and stir for 1hr. The precipitated solid is filtered and washed with 20ml ethyl acetate to get 20g wet crude Dex-brompheniramine maleate.

4) Purification of crude Dex-Brompheniramine Maleate
The filtered wet cake is leached with 45ml ethyl acetate at 0°C for 1 hr and filtered to get 18g of pure Dex-brompheniramine maleate. The wet solid is dried under vacuum below
layer and extract with 25ml o-xylene. Combine both the o-xylene layers and wash with water (25ml x 2). Distill out o-xylene 50-55°C. (Yield=86.7%, M.P.=112.4°C, SOR=+37.03° c=5% Dimethyl formamide, chiral purity=99.5%).

5) Recovery and racimisation of Levo-brompheniramine
Take methanol filtrate from resolution and distill out under vacuum below 50°C to get 80g of PNTA salt of Levo-Brompheniramine, treated with 80ml Hydrochloric acid in 240ml of DM Water under stirring for 4 hrs at room temperature. The precipitated solid is filtered to get PNTA. The recovered PNTA is recycled for further use. The filtrate aqueous is basified by 50% caustic solution till pH becomes 9.0-9.5 at room temperature. The basified aqueous is extracted by o-xylene (150ml x 3). Distill out o-xylene under vacuum and degass to get 25g Levo-Brompheniramine base.

To 25g Levo-Brompheniramine base add 10g of potassium hydroxide flakes and heat to 140-150°C for 8-10 hrs. Cool reaction mass to room temperature add 35ml water and 35ml o-xylene, stir for 30mins, settle for 30mins and separate o-xylene layer and keep it aside. Take aqueous completely under vacuum to get 22g crude Brompheniramine base. High vacuum distillation (HVD) of crude Brompheniramine base is done to get 15g pure Brompheniramine base. (Ist fraction below 170°C, IInd fraction between 160-180°C and IIIrd fraction above 180°C).

RESULTS AND DISSCUSSION
To confirm the elemental composition of Dexbrompheniramine Maleate, it was subjected to CHN analysis and the values obtained were compared with the theoretical values calculated from the molecular formula CI6H19BrN2. C4H4O4 of Dexbrompheniramine Maleate(Table-I).

Table-I: Elemental Composition data of Dexbrompheniramine Maleate

Molecular Formula	Formula Weight	Elemental Composition Found(Calculated)			
		C	H	N	O
C16H19Br N2.C4H4 O2	435.32	55.25% (55.18%)	5.268% (5.33%)	6.51% (6.44%)	14.70% (14.70%)

Mass spectrum of Dexbrompheniramine Maleate shows a molecular Ion Peak at 321 which is the value obtained theoretically after the protonation of one hydrogen atom in the calculated molecular mass of 319 using the molecular formula $C_{16}H_{19}BrN_2$. The UV spectrum of Dexbrompheniramine Maleate in 0.1 M Hydrochloric Acid at concentration of 32.5ppm exhibits peak maxima at 265 nm. Assignment of various frequencies obtained from the FTIR spectrum to their corresponding functional groups is depicted in Table-II. The assignment of the chemical shifts and the number of protons in the molecule has been described in Table-III and Table-IV.

Table-II: FTIR data of Dexbrompheniramine Maleate

Wave Number (cm^{-1})	Functional group / Band assignment
2957.64-3046.93	Aromatic and unsaturated C-H stretch
2470.33-2696.98	N-H stretch
1586.90	Aromatic C=N stretch
1480.01	Aromatic C=C, C=N, carboxylate C-O stretch
1434.72	Carboxylate C-O stretch
864.54	Maleate

Table-III: 1H-NMR data of Dexbrompheniramine Maleate

Chemical shift (ppm)	Multiplicity	H atoms	Assignment
8.544 - 8.562	Multiplet	1H	Pyridine ring
7.561 -7.604	Multiplet	1H	Pyridine ring
7.167 -7.427	Multiplet	4H	Bromobenzene ring
7.082-7.151	Multiplet	2H	Pyridine ring
6.264	Singlet	2H	-COOH of maleic acid
4.055 - 4.093	Triplet	1H	-CH-CH_2-CH_2-N-$(CH_3)_2$
2.751 - 3.005	Multiplet	4H	-CH-CH_2-CH_2-N-$(CH_3)_2$
2.400 - 2.440	Triplet	6H	-CH-CH_2-CH_2-N-$(CH_3)_2$

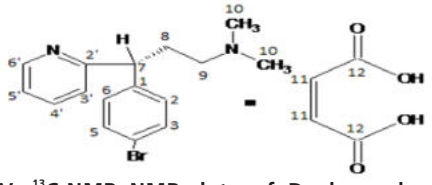


Table-IV: ^{13}C-NMR NMR data of Dexbrompheniramine Maleate

Chemical shift (ppm)	Position of Carbon
28.97	8
42.63	10
49.68	9
56.27	7
121.14	5'
122.16	3'
123.49	3,5
129.37	2,6
131.98	4
135.45	11
136.96	4'
140.80	1
149.27	6'
160.21	2'
169.44	12

CONCLUSION

1. 4-nitro tartranilic acid(PNTA) gives better separation of enantiomers.
2. Both 4-nitro tartranilic acid and another Isomer can be recycled and reused during the process thus fulfilling the principle of Green Chemistry.
3. The Analytical and spectral data like UV, FTIR, ^{1}H-NMR, ^{13}C-NMR and Mass analysis of Dexbrompheniramine Maleate confirms the predication for the chemical structure as per literature[11-13].

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