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SYNTHESIS OF (2E)-DEHYDROPROPAFENONE HYDROCHLORIDE

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ABSTRACT
Propafenone is a well-known anti-arrhythmic drug. During the synthesis of Propafenone some structurally related compounds are formed as impurities which is to be identified, since some of the impurities formed may decrease the activity or a threat to the usage of the drug. So characterization of such impurities very much needed for better therapeutic index. One such impurity is (2E) - dehydro propafenone hydrochloride which is synthesized by aldol condensation.
Keywords: 2-hydroxy acetophenone, epichlorohydrin, propylamine and benzaldehyde.

INTRODUCTION

Propafenone (2'-3 propylamino)-2-(hydroxy) propoxy-3 propiophenone) hydrochloride, reported in the late 60's, displays the properties of β -adreno receptor blockers. Besides β -blocking properties,' the drug exhibits class slow channel (Ca++), IC antiarrhythmic action and blocking properties[1]. An accidentally taken, small dose of propafenone can aggravate obtrusive airways disease in the patient[2]. It is a beta-adrenergic blocker that causes a slow heart beat and difficulty in breathing[3]· Propafenone has caught the attention of the researchers because of its chemosensitizing activity in multi-drug resistant tumor cells[4].Propafenone was synthesized from 1-(2-hydroxyphenyl)-3-phenyl-1-Propanone and O-hydroxy acetophenone[5].

EXPERIMENTAL

Reagents and solvents used were received from various vendors. Reactions were monitored by using thin layer chromatographic (Merck TLC) plates. FT-IR measured as KBr pellets using Jasco.[1] H and [13]C-NMR spectra were obtained in CD_3OH at 300 MHz, using tetramethylsilane as the internal standard. Mass spectrum taken using scan mode by electron ionization technique.

Preparation of 2-(2', 3'-epoxypropoxy) - acetophenone

Two liter four necked round bottom flask equipped with condenser is charged with 200g(1469mmol) of 2'-hydroxy acetophenone, 1470ml of epichlorohydrin and 58.8g(mmol) of sodium hydroxide pellets were refluxed for 4 hours[7].After reflux cool to 25-35°C and then filtered. The filtered solution is concentrated to dryness. Pale yellow oily Liquid is obtained. Wt. = 250g

Preparation of 2-(2'-hydroxy-3'-propylaminopropoxy) acetophenone oxalate

70g of 2-(2', 3'-epoxypropoxy)-acetophenone (364mmol) and 300ml of n-propyl amine were refluxed for 4 hours. Cool and distill off excess n-propyl amine and then dissolve in 200ml of methanol at 50-60°C. Oxalic acid solution (60g of oxalic acid anhydrous dissolved in 500ml methanol) added at 50-60°C, stir for 20 minutes. Cool to 20-25°C and stir for 30 minutes. The solution is filtered and concentrated to dryness. Pasty mass is obtained and the mass is dissolved in 700ml of acetone methanol mixture in the ratio of 80:20 (V/V). Slowly cool to 25-30°C and stirred for 12 hours. The solid formed is filtered and dried.

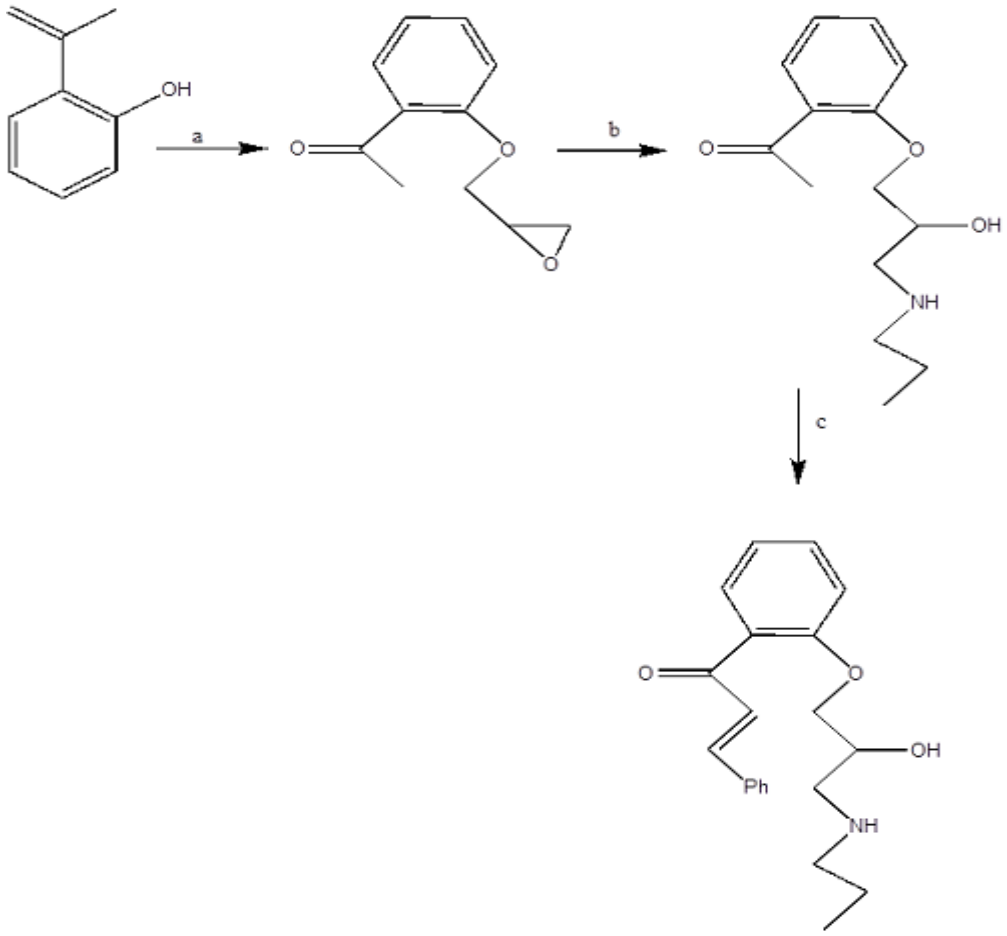
Preparation of dehydropropafenone hydrochloride

30g of Oxalate salt, dissolved in 340ml of Methanol at 50°C. Caustic solution (12g of sodium hydroxide dissolved in 22.5ml of DM water) slowly added for 10-15 minutes at 50-55°C. 8.0g of benzaldehyde add and heated to reflux for 4-5 hours and then cool to 30°C. Distill off methanol completely under vacuum.1N hydrochloride, 750ml add at 50°C and stir for 45mintues clear solution is obtained wash with 150ml of Methyl tertiary butyl ether. The aqueous layer's pH adjusted to 12 by 32% sodium hydroxide solution and again extracted with ethyl acetate. Ethyl acetate layer dried by sodium sulphate. The clean layer concentrated at 55-60°C to get dehydropropafenone as a free base. Add 150ml of toluene to the above base at 50-60°C. Concentrated HCl (about 30-32%), 6ml added at 55-60°C. Stir for 20-30 minutes at 55-60°C. The whole toluene mass concentrated under vacuum at 55-60°C. A residue obtained is dissolved in acetone and stir for 10 minutes. Distill out acetone completely and again add acetone (60ml) and methanol (2ml) and stir at 40-45° for 10 minutes then cool to 0-5°C for and 2 hours. The solid formed is filtered and washed with acetone. Its weight is 3.6g.

^{1}HNMR(300MHz,CD_3OD):δ7.70(2H,m),7.63(1H,d),7.57(2H,m),7.48(1H,d),7.42(3H,m),7.14(2H,m),4.20 (3H,m),3.14(2H,m),2.70(2H,t),1.65(2H,m),0.9(3H,t)

^{13}CNMR(CD_3OD):194.65,158.25,145.06,135.92,134.63,131.78,131.30,130.10,129.89,129.74,127.70,122. 26,114.01,71.87,66.26,51.48,50.62,20.16,11.23.

IR (Cm^{-1}):L 3343, 3043, 3020, 2967, 2882, 1740, 1707, 1648, 1240, 780; MS m/z: 340(M+)



(a) Epichlorohidrin, Toluene, NaOH; (b) N-Propylamine; (c) Benzaldehyde, NaOH, HCl

Scheme-1

RESULTS AND DISCUSSION

Synthesis of Propafenone involves the reaction between hydroxy acetophenone (1) and epichlorohydrin[6] and the resultant product (2) was treated with propyl amine to afford a compound (3) which is then treated with benzaldehyde to give a corresponding chalcone (4) the resulting double bond is hydrogenated at 1 atm under hydrogen to furnish the desired product. During the synthesis of propafenone hydrochloride if the reaction is incomplete it forms an inseparable mixture with the desired product. The compound is identified to be dehydropropafenone the existence of this impurity is further confirmed by synthesis and supported by analytical methods.

REFERENCES

1. C. John Somberg, David Tepper and Stuart Landau, *American Heart Journal*, **115**,1274(1988).
2. D. Torres , G. Parrinello, S. Paterna ,M. Bellanca and G. Licata , *Am. J. Ther.,* January (2011).
3. L. A. Siddoway, D. M. Roden and R L. Woosley , *Am. J. Cardiol.*,**54**,9(1984).
4. P. Chiba ,S. Burghofer ,E. Richter ,B. Tell , A. Moser , and G. Ecker , *J. Med. Chem.*, **38**,2789(1995).
5. S. Marshall, Ed. Pharmaceutical Manufacturing Encyclopedia, New Jersey, Vol. 1, pp 1308(1988).
6. V. D.Patil and C.L. Viswanathan, *Indian Journal of Pharmaceutical Sciences*,**59**,98(1997).
7. R. M. Rowell and G. C. Chen , *Wood Science and Technology*,**28**, 371(1994).

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