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Research Article

SYNTHESIS OF PROCHLOROPERAZINE RELATED COMPOUND A IMPURITY FORMED DURING CHLORPROMAZINE DRUG PREPARATION

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ABSTRACT

In the present work identification and synthesis of Prochlorperazine related compound A impurity in the manufacture of API Chlorpromazine has been reported. Characterization of the product was done by H1 NMR spectral data. Identification of this impurity results in synthesis of pure Prochlorperazines drugs.

KEYWORDS: *Prochlorperazines, Impurity, Sulphur, API drug.*

INTRODUCTION

Phenothiazines [1] are very important class of organic compounds. Phenothiazines and their derivatives find a separate place for themselves in medicinal chemistry for acting as antipsychotic drugs. Phenothiazine drugs[2] were used in early 1950s and are still been used today. Chlorphenothiazines were found to show good antihelmintic activity.

Chlorpromazine belongs to a class of drugs called promazines which are phenothiazines having aliphatic side chain and is used to treat psychotic disorders in children. It is also used to prevent nausea and vomiting before surgery. They are a family of neuroleptic tranquilizer drugs first synthesized by Charpentier [2] et al., in 1950 as antihistamic drugs. Several impurities are seen in the synthesis of Chlorpromazine.

Prochlorperazines [3, 4] belongs to a class of drugs called perazines which are phenothiazines with piperazine side chain. It was later discovered as antiemetic (to control nausea and vomiting) and is a moderate potency typical antipsychotic drug. They act as a dopamine antagonist. Several impurities are seen during the synthesis of Chlorpromazine and prochlorperazine. To name a few are impurities like A, B, C, D and E with variations in their side chain (Fig. 1).

Prochlorperazine related compound A is also seen as one of the impurities in minor quantities. Herein we present a synthetic strategy for preparation of the Prochlorperazine related compound A so that it can be identified easily during prochlorperazine or other phenathezine synthesis.

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EXPERIMENTAL WORK

Step 1: Synthesis of 4-chloro phenothiazine (II):

To a mixture of 3-chloro diphenylamine (I, 10.2 g 0.05 mol) and redistilled sulphur (1.6 g 0.05 mol) was added 0.4 g of iodine and heated at 170 °C for 1 hr. Then distillation of the reaction mixture gave 6.3 g of light yellow coloured oil which solidified on cooling. Fractional crystallization from benzene light petroleum mixture gave two isomers. More soluble colourless plates of 4-chloro phenothiazine (II, 1.5 g, 13 %) was crystallized from light petroleum (m. p. 115 °C Found : 60.66 % C, 3.32 % H, 12.6 % S, Calc., 61.65 C, 3.40 % H, 13.1 %, S; H1-NMR ($CDCl_3$, 400 MHz) δ6.43 (1H, ddd, J=8.3, 1.2, 0.5 Hz), 6.50 (1H, dd, J=8.3, 1.3 Hz), 7.05-7.19 (3H, 7.13 (ddd, J=7.8,1.4. 0.5 Hz), 7.09 (ddd, J = 7.8,7.5,1.2 Hz), 7.17 (dd, J=8.1, 1.3 Hz)), 7.25 (dd, J=8.3, 8.1 Hz), 7.28 (ddd, J=8.3, 7.5, 1.4 Hz))); and less soluble yellow coloured plates of 2-chloro phenothiazine (III, 4.1 g, 35 % yield) which crystallized from benzene (m. p. 198 °C Found : 61.65 C, 3.40 % H, 13.1 % S; H1-NMR ($CDCl_3$, 400 MHz) δ 6.43 (1H, ddd, J=8.3, 1.2, 0.5 Hz), 7.05-7.16 (2H, 7.13(ddd, J=7.8, 1.4, 0.5 Hz), 7.09 (ddd, J=7.8, 1.4, 0.5 Hz), 7.17-7.36 (3H, 7.33 (dd, J=8.3, 0.5 Hz, 7.28 (ddd, J=8.3, 7.5, 1.4 Hz), 7.20 (dd, J=8.3, 7.5, 1.4 Hz), 7.20 (dd, J=8.3, 1.7 Hz)), 7.68 (1H, dd, J=1.7,0.5 Hz)). Compound II shows two peaks in IR at 750 and 774 cm^{-1} while compound III shows a peak at 808 cm^{-1}.

Step 2: Synthesis of 4-Chloro-10-(3-chloropropyl)-10H-phenothiazine (IV):

Compound II (1.0 g, 4.28 mmol, 1 equiv.) was dissolved in 15 ml of anhydrous DMF at room temperature for 10 minutes. To this 1-bromo-3-chloropropane (742 mg, 4.71 mmol) and sodium hydride (108 mg, 4.71 mmol, 1.1 equiv.) were added. The resulting solution was stirred at room temperature

overnight. The reaction mixture is then quenched with brine and extracted with ethyl acetate. The organic layers are then combined, washed with brine and dried over Na2SO4 to obtain 1.2 g of light yellow oil. It is then purified by column chromatography using benzene - ethyl acetate over silica gel (5:1) to give 1.11 g of pure compound IV with 84% yield. H1-NMR (CDCl3, 400 MHz) δ 2.35 (2H,tt, J=7.8, 6.9Hz), 3.61 (2H, t, J=7.8 Hz), 3.62 (2H, t, J=6.9 Hz)), 6.39 (1H, ddd, J=8.3, 1.2, 0.5 Hz), 6.46 (1H, dd, J=8.3, 1.3 Hz), 7.02 (1H, ddd, J=7.9, 7.5, 1.2 Hz), 7.12 (1H, ddd, J=7.9, 1.4, 0.5 Hz), 7.25 (dd, J=8.3, 8.1 Hz), 7.24 (ddd, J=8.3,7.5,1.4 Hz), 7.22 (dd, J=8.1, 1.3 Hz)).

Step 3: Synthesis of 4-Chloro-10-[3-(4-methylpiperazin-1-yl) propyl]-10H-phenothiazine (V):

Compound IV (500 mg, 1.61 mmol, 1 equiv) was dissolved in 10 ml of anhydrous DMF at room temperature for 10 minutes. To this N-methyl piperazine (178 mg, 1.77 mmol, 1.1 equiv.) is added and stirred for 10 minutes. The temperature is slowly raised to 100 °C and stirred for 8 hrs. The reaction mixture is then extracted with ethyl acetate. The combined organic layers were then washed with water to yield 850 mg of coloured oil. The obtained product is then chromatographed using benzene - ethyl acetate over silica (4:1) to give 462 mg of pure compound IV with 77% yield. H1-NMR (CDCl3, 400 MHz) δ1.97 (2H, tt, J=4.6,2.7Hz), 2.38 (3H,s),2.49-2.63 (8H, 2.57 (ddd,J=10.2,7.8, 2.5Hz), 2.53 (ddd, J=7.8,3.1,2.5 Hz)),2.69 (2H, t, J=2.7 Hz),3.58 (2H, t, J=4.6 Hz),6.39 (1H, ddd, J=8.3, 1.2,0.5 Hz),6.46 (1H, dd, J=8.3, 1.3 Hz), 7.02 (1H,ddd, J=7.9, 7.5, 1.2 Hz), 7.12 (1H,ddd, J=7.9, 1.4, 0.5 Hz), 7.19-7.30 (3H, 7.25 (dd, J=8.3, 8.1 Hz), 7.24 (ddd, J=8.3, 7.5,1.4 Hz), 7.22 (dd, J=8.1, 1.3 Hz)).

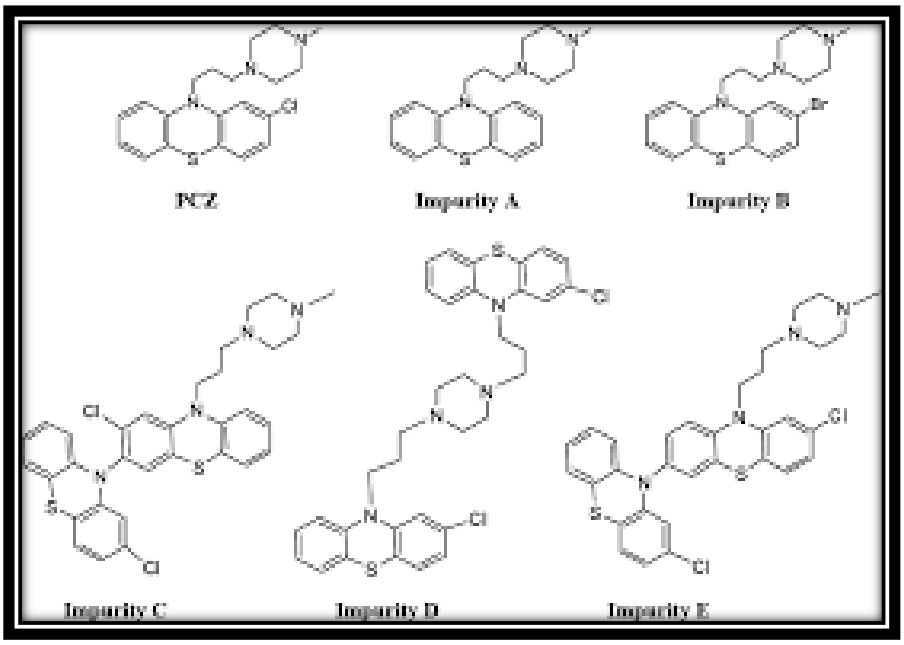
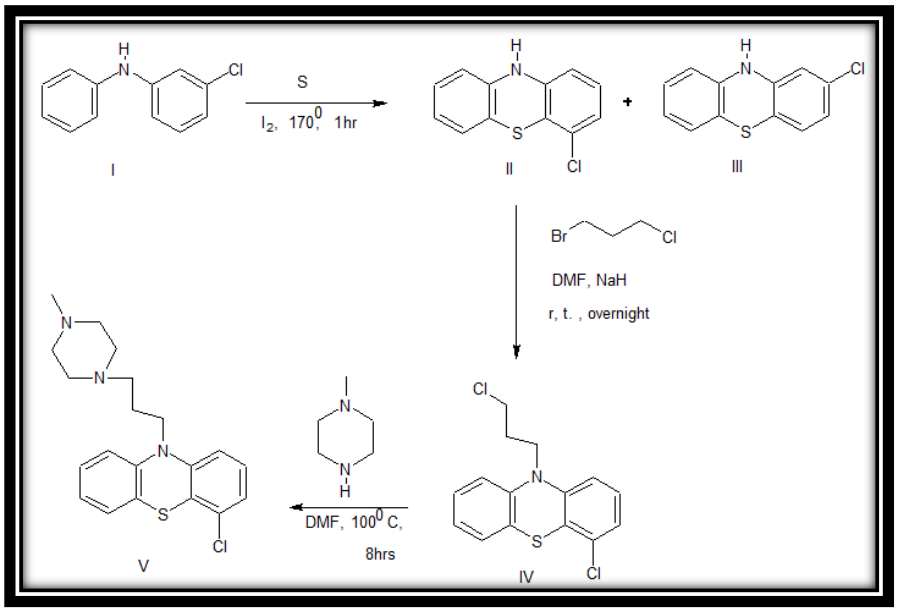


Fig. 1: Impurities in Chlorpromazine synthesis



Scheme 1: Synthesis of Prochlorperazine related compound A

RESULTS AND DISCUSSION

Materials: All materials were purchased from Sigma Aldrich. DMF of 98% purity was used as such without further purification

Methods: A fourier transform infrared spectrophotometer (FTIR:Shimadzu 4300 was applied to record the infrared spectra of samples by using KBr ellets in the range of 4000-400 cm-1. 1H NMR spectra were recorded at 4 MHz on a Bruker Avance 3 sectrometer and chemical shifts are given in ppm. Samples were measured at 20 C in 5 mm NMR tubes. Chemical shifts (ppm) are referred to TMS. Melting point was recorded on an electro thermal 9100 digital melting point apparatus 1A instrument.

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