

**A NEW SYNTHESIS OF PHENOTHIAZINES**

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**ABSTRACT**

Phenothiazine and its 3-methyl-, 3-chloro- and 5-nitro derivatives have been prepared by a new method which consists in the condensation of aniline, p-toluidine, p-chloro aniline and p-nitro aniline respectively with cyclohexanone followed by heating the resultant Schiff bases with sulphur at 260-280 °C for six to eight hours. The compounds have been identified by comparison with authentic samples.

**KEYWORDS:** Phenothiazine, Antipsychotic, Antihistaminic, Schiff's base, Diphenylamine, Sulphur

**INTRODUCTION**

Phenothiazine (Fig. 1), related to the thiazine-class of heterocyclic compounds, is very important as it occurs in various antipsychotic and antihistaminic drugs. The compound has also been variously used as an anthelmintic and insecticide.<sup>1</sup> Derivatives of phenothiazines are useful as urinary antiseptics, tranquilisers<sup>2</sup> and anti-oxidants in high temperature lubricants.<sup>3</sup> There are a good number of methods of preparation and these have been reviewed.<sup>4</sup>

One of the most important methods of preparation consists in the heating of suitable substituted diphenylamines with sulphur. (Fig.2)

The obvious drawback of this method and several other methods described in literature is the difficult availability of the starting materials.<sup>5-12</sup>

Association of some important amphiphilic phenothiazine drugs in aqueous solution was studied to enrich understanding the drug action mechanism.<sup>13</sup> Phenothiazine based donor- $\pi$ -acceptor dyes for efficient dye-sensitized solar cells are now being studied through practical applications.<sup>14-17</sup> Phenothiazine moieties in redox active polymers for nanoscale patterning is also recently reported *via* conductive scanning force microscopy.<sup>18</sup>

**MATERIALS AND METHODS**

A mixture of aryl amine (1 mole) and cyclohexanone (1.1 mol) in dry benzene was heated in a Dean Stark water separator until no more water separated. Removal of the solvent followed by fractionisation under reduced pressure gave the Schiff bases in appreciably good yields.

The Schiff base was heated with excess of sulphur in a Wood's metal bath at 260-280 °C for six to eight hours. The reaction mixture was cooled and the phenothiazine extracted with benzene. Concentration of the extract followed by sublimation gave the phenothiazine. Further purification was done by crystallization from benzene-petroleum ether. The results are shown in Table 1.

**RESULTS AND DISCUSSION**

Schiff bases derived from aryl amines and cyclohexanone can be a source of diphenylamine. The easy availability of a number of substituted aryl amines can therefore be easily exploited in the synthesis. It was anticipated that heating these Schiff bases with sulphur at high temperatures would produce phenothiazines, probably by way of diphenylamines produced *in situ*. We, therefore, have

prepared some Schiff bases using aniline, p-toluidine, p-chloroaniline, p-nitroaniline and cyclohexanone. The Schiff bases were heated with sulphur in a metal bath at 260 to 280 °C for period ranging from six to eight hours. The phenothiazines were obtained (Scheme 1) in yields ranging from 10 to 30%. We are extending the method for the preparation of other phenothiazine derivatives. The compounds were identified by comparison with authentic samples.

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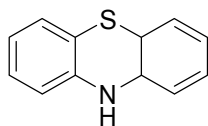
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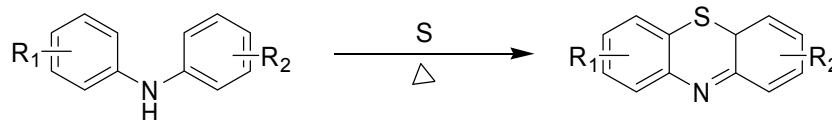
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**Table 1.** Synthesis of phenothiazine derivatives.

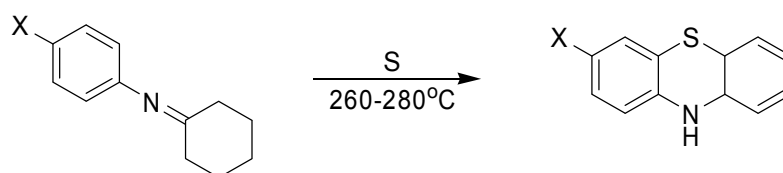
Entry	Schiff's Base	Yield (%)	M.P. (°C)	Lit. M.P. (°C)	Ref.
1	H	18	178	180-81	5
2	CH <sub>3</sub>	20	167	166-68	6,7
3	Cl	30	195	199	8,9
4	NO <sub>2</sub>	10	218	218	10,11



**Fig. 1** Phenothiazine



**Fig. 2** General preparation of phenothiazines



X= H, CH<sub>3</sub>, Cl, NO<sub>2</sub>

**Scheme 1.** Preparation of phenothiazines from Schiff's bases.

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