Phenothiazine Derivatives. V[1]. Synthesis of Hydroxyphenothiazines

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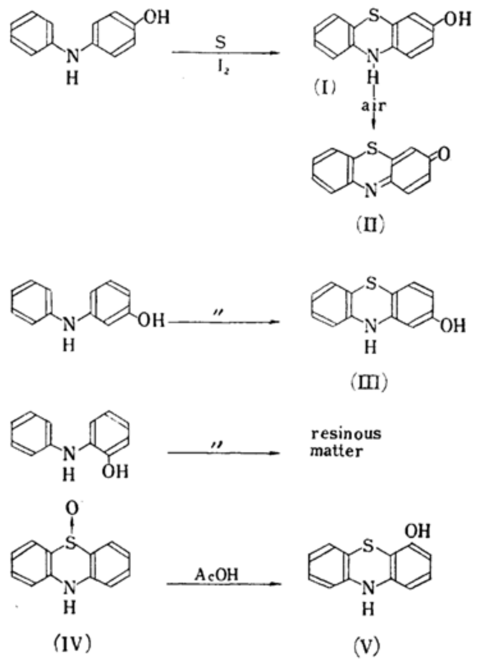
Of the theoretically possible four hydroxyphenothiazines, the 3-hydroxy compound I only has been reported[2,3]. By treating 4-hydroxydiphenylamine with sulfur and iodine, Houston et al.[2] prepared the compound as a dark greenish brown solid with m. p. 170~175°C and with a tendency to be easily oxidized in air to 3-phenothiazone (II) (Chart I).

Before Houston et al., Hilditch and Smiles already prepared the supposed 3-hydroxyphenothiazine[3] by an intramolecular rearrangement of phenothiazine 5-oxide in acetic acid. It was a purple crystalline mass that defied purification. They submitted it to reduction with zinc and hot acetic acid and obtained a colorless soft crystalline substance which rapidly recovered purple color in the presence of air.

Chart I



The present author repeated the experiment of Hilditch and Smiles and obtained a reddish-violet substance in fine powder melting at 141~143°C. It showed a distinct depression of the melting point on admixture either with 3-hydroxyphenothiazine (I) or with 3-phenothiazone (II), prepared according to the method of Houston et al[2]. Although the rearranged product was chromatographically pure and phenolic in nature, it was evidently different from the substances of Houston et al.

The investigation described below presents a contribution to the solution of the problem concerned. In the first place, an attempt was made to synthesize all of the unknown hydroxyphenothiazines.

It was reported by Charpentier et al.[4] that the reaction of a *meta* substituted diphenylamine with sulfur and a small amount of iodine as a catalyst gives a mixture of a 2-substituted phenothiazine and its 4-isomer, although the 2-substituted product is formed in a greater yield, and that 3-methoxydiphenylamine gives only 2-methoxyphenothiazine.

The present author obtained one hydroxyphenothiazine by thionation of 3-hydroxydiphenylamine, but could not isolate the expected isomeric product. Therefore, the hydroxyphenothiazine is supposed to be 2-hydroxyphenothiazine (III). As a very unstable compound, 2-hydroxydiphenylamine gave only a black resinous matter by a similar treatment. If 1-hydroxyphenothiazine, were obtained by the reaction of 2-hydroxydiphenylamine it would have a tendency to form 1-phenothiazone similarly to the 3-hydroxy isomer I.

As an alkaline solution of the substance, obtained by the intramolecular rearrangement of phenothiazine 5-oxide IV with acetic acid according to Hilditch and Smiles resists aeration, it is considered to be a phenol with the hydroxyl group in a *meta* position to the nitrogen atom. Two such hydroxyphenothiazine are possible,

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[1] Part IV: This Bulletin, **32**, 296 (1959).

[2] D. F. Houston et al., *J. Am. Chem. Soc.*, **71**, 3818 (1949).

[3] T. P. Hilditch and S. Smiles, *J. Chem. Soc.*, **101**, 2295 (1912).

[4] P. Charpentier et al.: *Compt. rend.*, **235**, 59 (1952).

namely, 2-hydroxy- and 4-hydroxy-phenothiazines. As the substance from the rearrangement of the 5-oxide (IV) differs conspicuously from 2-hydroxyphenothiazine (III) described above, it must be 4-hydroxyphenothiazine (V). The position 4 is quite a reasonable place where the sulfoxide oxygen atom may migrate.

Experimental

3-Hydroxyphenothiazine (I) and 3-Phenothiazone (II). — Essentially the method of Houston et al.[2] was followed.

2-Hydroxyphenothiazine (III). — A mixture of 3.7 g. of 3-hydroxydiphenylamine and 1.4 g. of sulfur was ground in a mortar and placed in a 100 ml. flask. Then 0.04 g. of iodine was added, and the flask was stoppered and placed in a metal bath preheated to 190°C. The bath temperature was kept at 190∼200°C during 30 min., while hydrogen sulfide was evolved, and then for additional 10 min. The reaction mass was poured into a porcelain dish and allowed to cool. It solidified to a greenish-yellow cake. Yield, 4.2 g. Fractional recrystallization from benzene gave 3.2 g. of the pure substance III in dark yellow powder, m. p. 270∼272°C. It gives cobalt-blue coloration with sulfuric acid.

Anal. Found: C, 67.11; H, 4.09; N, 6.40. Calcd. for $C_{12}H_9ONS$: C, 66.85; H, 4.21; N, 6.50%.

4-Hydroxyphenothiazine (V). — Acetic acid (20 ml.) was added to phenothiazine 5-oxide (IV) (1.0 g.), and the reddish-violet solution was refluxed for 3 hr. Acetic acid was evaporated in vacuo, and the residue was recrystallized from absolute ethanol. The yield was quantitative. It forms reddish-violet fine powder, m. p. 141∼143°C, and gives sepia-brown coloration with sulfuric acid. It is soluble in 10% aqueous caustic soda. The benzene solution showed a single adsorption band in the chromatogram on alumina.

Anal. Found: C, 67.01; H, 4.08; N, 6.45. Calcd. for $C_{12}H_9ONS$: C, 66.85; H, 4.21; N, 6.50%.

Summary

The phenolic compound resulting from the rearrangement of phenothiazine 5-oxide in acetic acid was found to be 4-hydroxyphenothiazine, and to be different from 2- and 3-hydroxyphenothiazines which were derived from 3- and 4-hydroxydiphenylamines, respectively, by fusion with sulfur and iodine.

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