Phenothiazine Derivatives. III[1]. *Mechanism of the Reaction of Diphenylamine with Thionyl Chloride*

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In the preceding paper[1] of this series, it was reported that diphenylamine (I) reacts violently with thionyl chloride, thionyl bromide and sulfuryl chloride, and that thionyl chloride transforms diphenylamine (I) into 1, 3, 7, 9-tetrachlorophenothiazine (II), while thionyl bromide and sulfuryl chloride transforms it merely into 2, 4, 6, 2′, 4′, 6′-hexabromodiphenylamine and the corresponding hexachlorodiphenylamine (III), respectively, as shown schematically in Chart I, where arrows with crosses indicate that the expected changes do not take place by the action of thionyl chloride.

Thionyl bromide is less stable than thionyl chloride, decomposing slowly even at room temperature as follows:

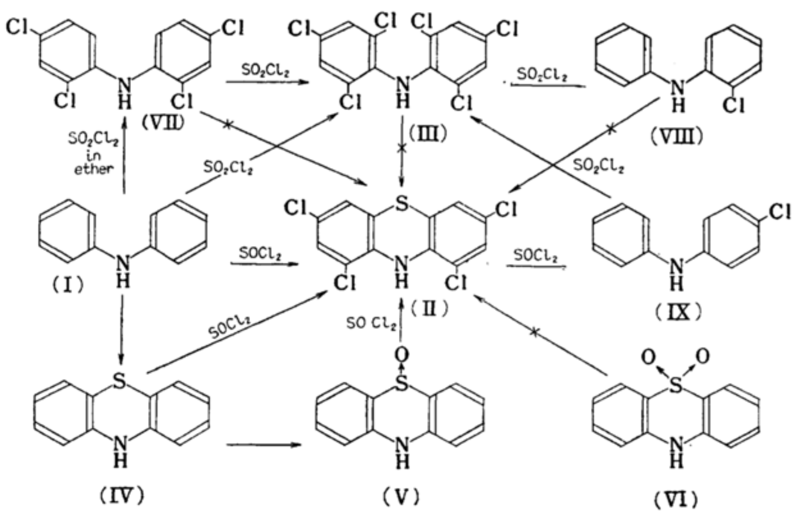
$$4SOBr_2 \rightarrow S_2Br_2 + 3Br_2 + 2SO_2$$

Therefore, in its reaction with diphenylamine (I) it gives an extensively brominated product, hexabromodiphenylamine. On the other hand, the sulfonyl group in sulfuryl chloride is so stable that the reagent can react with diphenylamine (I) only as a chlorinating agent (Chart I).

The present paper deals with the characteristic reaction of thionyl chloride with diphenylamine which has been further studied closely. The reaction involves at least two processes, namely, phenothiazine ring formation and chlorination of the benzene nuclei, but the sequence of the two processes is to be determined.

As already reported[1], phenothiazine (IV) and its 5-oxide (V) react with thionyl chloride to form the same tetrachlorophenothiazine (II). Nevertheless, it has now been found that the hexachlorodiphenylamine (III), 2, 4, 2′, 4′-tetrachlorodiphenylamine (VII)[2], 2-chlorodiphenylamine (VIII) and phenothiazine 5, 5-dioxide (VI) do not react with thionyl chloride. On the other hand, the tetrachlorophenothiazine (II) was obtained from the reaction of 4-chlorodiphenylamine (IX) and thionyl chloride. Therefore, it may be concluded that the first process of the reaction giving the chlorinated phenothiazine is the sulfur-bridge formation to

CHART I



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[1] Part II; H. Kanô and M. Fujimoto, *Pharm. Bull.*, **5**, 393 (1957).

[2] F. Krollpfeiffer et al., *Ber.*, **67**, 914 (1934).

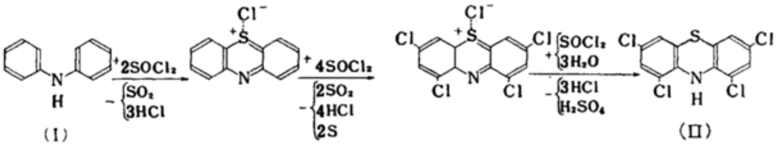
TABLE I

Solvent	Thionyl chloride (g.)	Volume of solvent (ml.)	Time of reflux	Recovered diphenylamine (%)	Diphenylamine hydrochloride (%)	Tetrachloro-phenothiazine (%)
Benzene	0.7	30	1 hr.	71	26	2
	4.2	〃	〃	78	—	10
Carbon tetrachloride	0.7	20	〃	80	13	—
	4.2	〃	30 min.	58	33	—
	〃	〃	8 hr.	57	—	28

give the phenothiazine ring system, followed by the chlorination to yield the final product II.

It was expected that dilution with an inert solvent, such as benzene or carbon tetrachloride, might moderate the reaction and make it possible to catch an intermediate of the phenothiazine type, such as phenothiazine (IV), its 5-oxide (V), phenazathionium chloride or hydroxide. But moderation of the reaction gave mainly diphenylamine hydrochloride along with a small amount of the final product II (Table I). This result can be interpreted by assuming that the dilution with an inert solvent retards greatly the first process of phenothiazine formation, but the chlorination of the phenothiazine once formed is relatively rapid.

In the reaction of diphenylamine to give the tetrachlorophenothiazine (II), color development of brown to dark green and the presence of sulfur monochloride or dichloride in the thionyl chloride in reflux are always observed, which facts suggest intermediate formation of phenazathionium chloride, because it is known that penazathionium chloride and hydroxide form dark brown needles[3]. Thus the reaction mechanism may be represented as follows:



As phenothiazine 5,5-dioxide is a sulfone, so it would not be transformed into a phenazathionium compound, and thus it can reasonably be expected that it will resist the attack by thionyl chloride.

Experimental

Treatment with Thionyl Chloride. — The general procedure for the treatment with thionyl chloride was as follows. To a diphenylamine or a phenothiazine derivative (1 g.), 10 ml. of thionyl chloride was added dropwise, and the mixture was heated gently under reflux for 5 min. Hydrogen chloride and sulfur dioxide were evolved when a reaction took place. The cooled solution was poured onto crushed ice. 1,3,7,9-Tetrachlorophenothiazine (II) was obtained yellow crystals from diphenylamine (I), phenothiazine (IV), the 5-oxide (V) and 4-chlorodiphenylamine (IX). Recrystallized from benzene, it showed m.p. 235~236°C. The yield was nearly quantitative. 2,4,6,2′,4′,6′-Hexachlorodiphenylamine (III), 2,4,2′,4′-tetrachlorodiphenylamine (VII), 2-chlorodiphenylamine (VIII) and phenothiazine 5,5-dioxide (VI) were recovered intact.

Treatment of Diphenylamine with Thionyl Chloride in Solution. — Diphenylamine (1 g.) was dissolved in a solvent, and thionyl chloride dissolved in the same solvent was added drop by drop. The mixture was refluxed, cooled, and poured on ice. After filtration, the organic layer was separated, dehydrated over sodium sulfate, and passed through a column of alumina. Elution first with the same solvent and then with a mixture of the solvent and acetone gave the results listed in Table I.

Diphenylamine Hydrochloride. — Recrystallized from methanol-ethyl acetate. Colorless needles, m.p. 195~196°C (decomp.).

Anal. Found: C, 69.80; H, 5.96; N, 6.75. Calcd. for $C_{12}H_{12}NCl$: C, 70.04; H, 5.88; N, 6.81 %.

Treatment with Sulfuryl Chloride. — One gram of each of diphenylamine (I), and chlorinated diphenylamines, VII, VIII and IX, was treated with 10 ml. of sulfuryl chloride. When the initial violent reaction ceased, the solution was refluxed for 30 min., and poured onto crushed ice. The precipitate was collected, dried, and recrystallized from ethanol. The product was always 2,4,6,2′,4′,6′-hexachlorodiphenylamine (III) which was obtained in colorless needles, m.p. 138~139°C. The yield was quantitative. 2,4,2′,4′-Tetrachlorodiphenylamine (VII) was prepared from diphenylamine by the action of sulfuryl chloride in ethyl ether[2]. Colorless needles, m.p. 141~142°C (from acetic acid). Yield, 74%.

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[3] E. de B. Barnett and S. Smiles, *J. Am. Chem. Soc.*, **95**, 1255 (1909).

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