H, 5.46; N, 7.99. Found: C, 57.85; H, 5.40; N, 8.11.

Hydrochloride: Colorless needles (from water), m.p. 209~211°. *Anal.* Calcd. for $C_{17}H_{20}O_2Cl_2S \cdot H_2O$: C, 50.36; H, 5.47; N, 6.91. Found: C, 50.70; H, 5.47; N, 7.06.

Picrate: Yellow needles, m.p. 236~237° *Anal.* Calcd. for $C_{23}H_{22}O_8N_5ClS \cdot H_2O$: C, 47.47; H, 4.16; N, 12.04. Found: C, 47.81; H, 4.19; N, 12.09.

2-Chloro-10-(3-dimethylaminopropyl-N-oxido)phenothiazine 5-Dioxide (XI)—The free base of (X) (2.7 g.) in 30 cc. of EtOH was added to 1.0 cc. of 30% H_2O_2, the solution was refluxed for 2 hrs., the solvent was evaporated, and 30 cc. of water and also a little of MnO_2 were added. The mixture was filtered and the filtrate concentrated, from which (XI) was obtained as a yellowish oil. Yield, 2.8 g.(99%).

Hydrochloride: Very hygroscopic colorless needles.

Picrate: Yellow needles (from $CHCl_3$), m.p. 204~205°(decomp.). *Anal.* Calcd. for $C_{23}H_{22}O_{10}N_5ClS$: C, 46.35; H, 3.72; N, 11.75. Found: C, 46.74; H, 3.98; N, 11.91.

Summary

The synthesis of theoretically possible four derivatives of chlorpromazine was described, in which the ring sulfur and then the nitrogen of lateral side chain were oxidized. The sulfone derivatives could not be derived from chlorpromazine itself, but could be prepared by the condensation of N,N-dimethyl-3-chloropropylamine with 2-chlorophenothiazine 5-dioxide, which was easily synthesized via 2-chloro-10-acetylphenothiazine.

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67. **Hideo Kano and Manabu Fujimoto**: Phenothiazine Derivatives. II.* Formation of Polychlorophenothiazines from Diphenylamines with Thionyl Chloride.

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One of the most convenient methods of preparing phenothiazines has been the ring closure reaction between diphenylamines and sulfur or sulfur halide. This reaction, referred to as thionation, has been widely used to synthesize many substituted phenothiazines.[1] We present in this paper studies on the reactivity of thionyl and sulfuryl halides on some diphenylamines.

Evolving sulfur dioxide and hydrogen chloride, diphenylamine (I) reacted violently in a large volume of thionyl chloride and from the final green product, yellow needles, m.p. 233~235°, were obtained. This was identified with an authentic sample of 1,3,7,9-tetrachlorophenothiazine (IV), prepared from (I), via (II), (III), and (IV).[2]

The same reaction also occurred in the case of (II) and (III). Therefore, the reaction of (I) might be as follows:

$$C_{12}H_{11}N + 6\ SOCl_2 \longrightarrow C_{12}H_5NCl_4S + SCl_2 + 3\ SO_2 + 6\ HCl$$

The sulfoxide derivative (V) of (IV) had m.p. 220~222°(decomp.)[3] and the sulfone (VI), m.p. 229°(decomp.). In the case of thionyl bromide, a tetrabromo derivative was not formed and the compounds formed another highly brominated compound, 2,4,6,2′,4′,6′-

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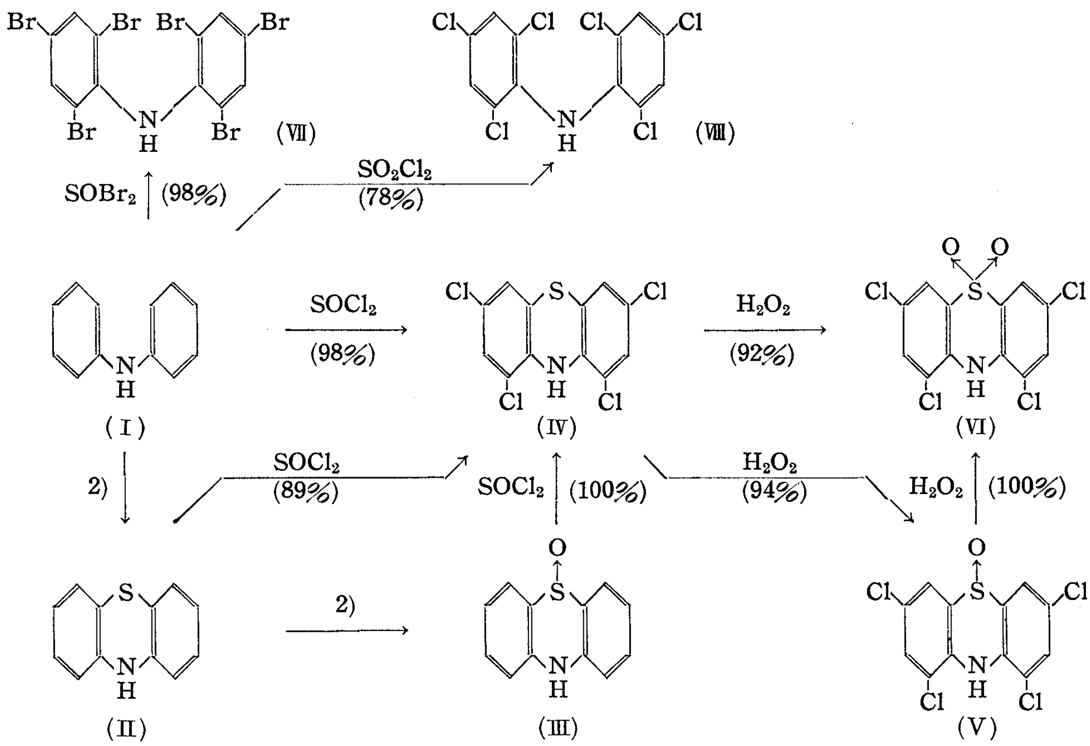
* Part I. This Bulletin, **5**, 389(1957).

** 192 Imafuku, Amagasaki, Hyōgo-ken (加納日出夫, 藤本 学).

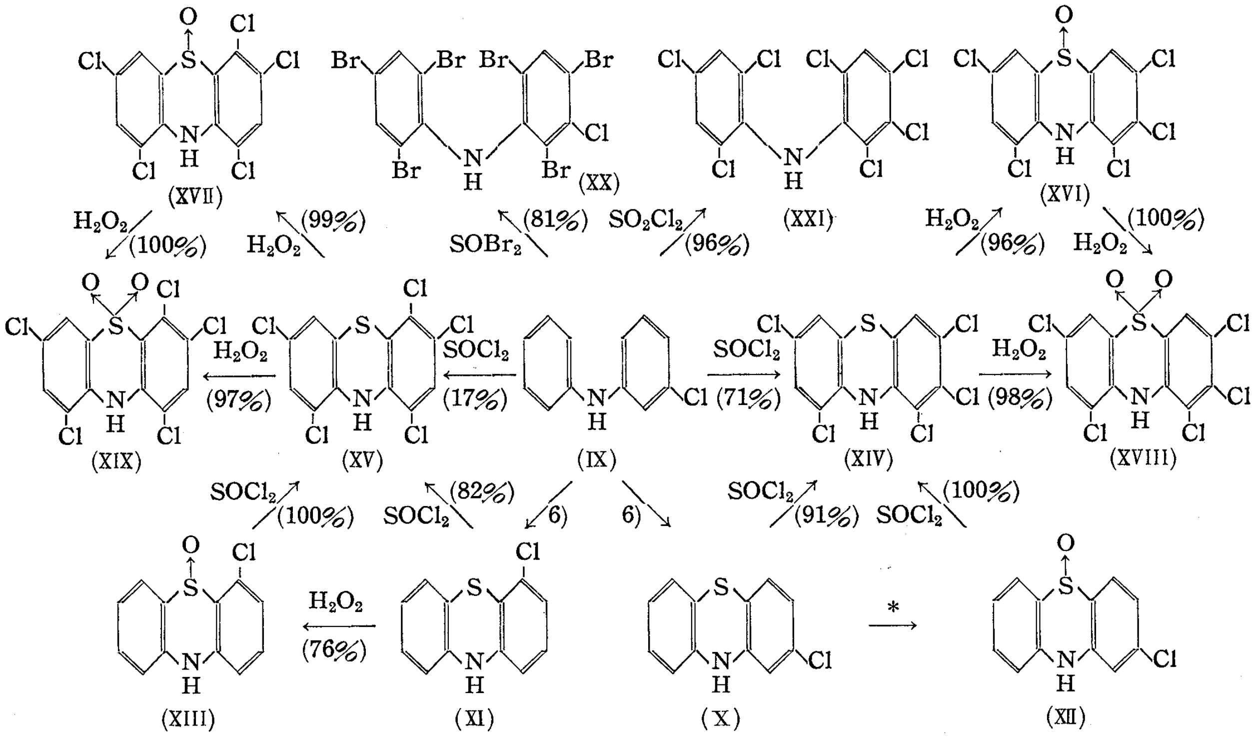
1) cf. S.P. Massie: Chem. Revs., **54**, 800(1954).

2) Schmalz, Burger: J. Am. Chem. Soc., **76**, 5455(1954).

3) Brady, Smiles: J. Chem. Soc., **97**, 1560(1910).



hexabromodiphenylamine (VII), m.p. 222~223°.[4] Sulfuryl chloride acted merely as a potent chlorinating reagent and gave a completely chlorinated diphenylamine, 2,4,6,2′,4′,6′-hexachlorodiphenylamine (VIII), m.p. 138~139°.[5] In order to investigate further the reaction of this type, 3-chlorodiphenylamine (IX) was reacted with thionyl chloride, thionyl bromide, and sulfuryl chloride.



Charpentier, *et al.*, in their studies on phenothiazine drugs, had considered the

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4) Elson, *et al.* : *Ibid.*, **1929**, 1085.
5) Chapman : *Ibid.*, **1929**, 571.

orientation of *meta*-substituted diphenylamines in thionation and determined that (IX) gave 2- and 4-chlorophenothiazines (X and XI).[6] In the present case, the reaction of thionyl chloride on (IX) gave a mixture of two polyhalogenated phenothiazines that could be separated by column chromatography on alumina (eluting with benzene). The first product of m.p. 204~205°, obtained in ralatively high yield (71%), was identified with 1,2,3,7,9-pentachlorophenothiazine (XIV) from (X) or (XII), and the second compound was 1,3,4,7,9-pentachloro isomer (XV), m.p. 169~170°. The infrared absorption spectra of (IV), (XIV), and (XV) are shown in Fig. 1.

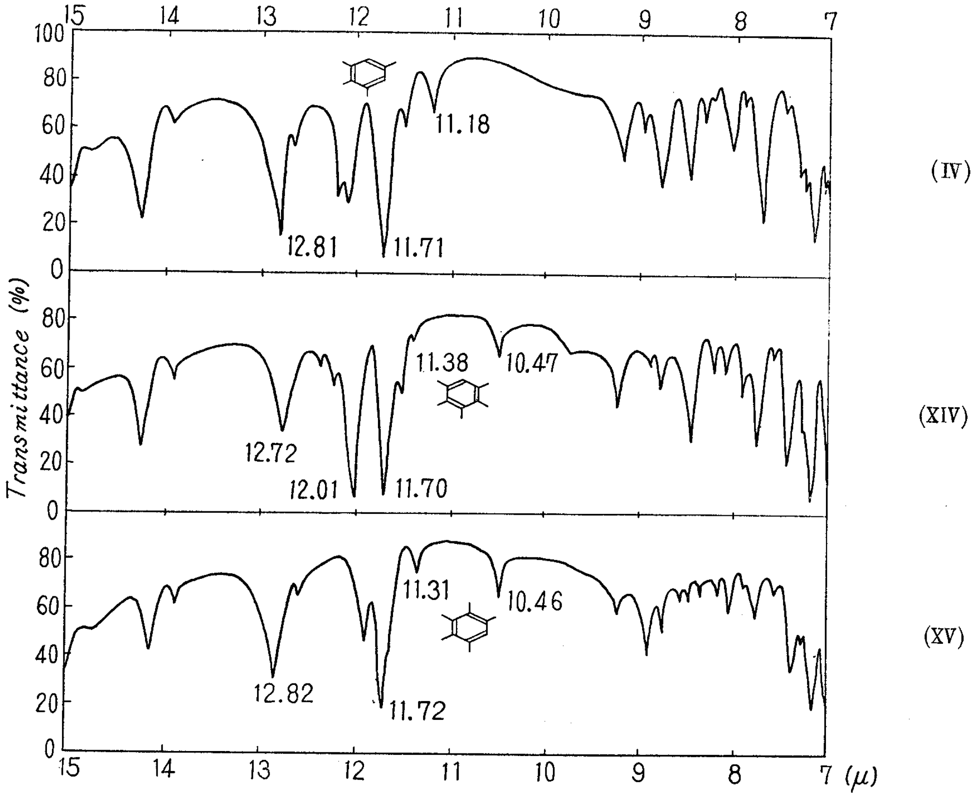

Fig. 1. Infrared Absorption Spectra (in Nujol)

The authors thank Dr. K. Takeda, the Director of this Laboratory, for permission to publish this paper, to Mr. Matsui for infrared absorption spectra, and also to the members of the Center of Microanalytical Service.

Experimental

1) **General Procedure of Ring Closure and Chlorination with $SOCl_2$**—Ten volumes of $SOCl_2$ was added dropwise to the compound to be chlorinated (such as diphenylamines, phenothiazines, or phenothiazine 5-oxides) and heated gradually under reflux for 30 mins., during which a gas mixture of HCl and SO_2 evolved. The cooled solution was poured on crushed ice. The yellow or green solid was collected, dried, and crystallised to give the polychlorophenothiazine as crystals.

1,3,7,9-Tetrachlorophenothiazine (IV)—Yellow needles (from dioxane), m.p. 233~235°.[2] Colors purple with H_2SO_4. *Anal.* Calcd. for $C_{12}H_5NCl_4S$: C, 42.77; H, 1.50; N, 4.16. Found : C, 42.51; H, 1.66; N, 4.56.

1,2,3,7,9-Pentachlorophenothiazine (XIV)—Colorless needles (from benzene), m.p. 204~205°. Colors reddish violet with H_2SO_4. *Anal.* Calcd. for $C_{12}H_4NCl_5S$: C, 38.80; H, 1.09; N, 3.77. Found : C, 38.83; H, 1.21; N, 4.06.

1,3,4,7,9-Pentachlorophenothiazine (XV)—Yellowish fine crystals (from EtOH-benzene), m.p. 169~170°. Colors blue-violet with H_2SO_4. *Anal.* Calcd. for $C_{12}H_4NCl_5S$: C, 38.80; H, 1.09; N, 3.77. Found. C, 38.54; H, 1.16; N, 3.86.

2) **Bromination with $SOBr_2$**—Twenty volumes of $SOBr_2$ was added to one volume of diphenylamine.

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[6] P. Charpentier, *et al.* : Compt. rend., **235**, 59(1952); French Pat. 1,029,987(1953).

After the initial violent reaction ceased, the mixture was warmed slightly to eliminate the excess of HBr-Br_2, poured on crushed ice, the precipitate was collected, and dried. The yellow crude product crystallised from $CHCl_3$.

2,4,6,2′,4′,6′-Hexabromodiphenylamine (VII)—Colorless plates, m.p. 222~223°.[4] *Anal.* Calcd. for $C_{12}H_5NBr_6$: C, 22.43; H, 0.78; N, 2.18. Found : C, 22.15; H, 0.74; N, 2.32.

3-Chloro-2,4,6,2′,4′,6′-hexabromodiphenylamine (XX)—Colorless prisms, m.p. 213~214°. *Anal.* Calcd. for $C_{12}H_4NBr_6Cl$: C, 21.28; H, 0.60; N, 2.07. Found : C, 21.17; H, 0.72; N, 2.25.

3) **Chlorination with SO_2Cl_2**—The same pattern of reaction as 2) was repeated.

2,4,6,2′,4′,6′-Hexachlorodiphenylamine (VIII)—Colorless needles (from EtOH), m.p. 138~139°.[5] *Anal.* Calcd. for $C_{12}H_5NCl_6$: C, 38.35; H, 1.34; N, 3.77. Found : C. 38.75; H, 1.70; N, 4.06.

2,4,6,2′,4′,5′,6′-Heptachlorodiphenylamine (XXI)—Colorless prisms (from EtOH), m.p. 146~147°. *Anal.* Calcd. for $C_{12}H_4NCl_7$: C, 35.13; H, 0.98; N, 3.41. Found : C, 35.21; H, 1.01; N, 3.83.

4) **Formation of some Sulfoxides**—A phenothiazine compound, such as (II),[2] (IV),[3], (X), (XI), (XIV), or (XV), was dissolved in a large amount of EtOH and reacted with 1 mole of 30% H_2O_2 on a water bath for 4 hrs. The mixture was concentrated, poured into water, and the crude sulfoxide obtained was recrystallised from adequate solvent.

4-Chlorophenothiazine 5-Oxide (XIII)—From 4-chlorophenothiazine, m.p. 118°,[6] (XIII) was obtained as colorless fine crystals (from dioxane), m.p. 241~243°(decomp.). Yield, 76%. Colors brown with H_2SO_4. I. R. $\lambda_{\max}^{\text{Nujol}}$: 9.99 μ (sulfoxide). *Anal.* Calcd. for $C_{12}H_8ONClS$: C, 57.73; H, 3.23; N, 5.61. Found : C, 57.43; H, 3.41; N, 5.67.

1,2,3,7,9-Pentachlorophenothiazine 5-Oxide (XVI)—Colorless fine crystals (from EtOH), m.p. 196~197°. *Anal.* Calcd. for $C_{12}H_4ONCl_5S$: C, 37.20; H. 1.04; N, 3.62. Found : C, 36.79; H, 1.27; N, 3.88.

1,3,4,7,9-Pentachlorophenothiazine 5-Oxide (XVII)—Colorless needles (from EtOH), m.p. 201~203°. *Anal.* Calcd. for $C_{12}H_4ONCl_5S$: C, 37.20; H, 1.04; N, 3.62. Found : C, 36.92; H, 1.30; N, 3.82.

5) **Formation of Some Sulfones**—The same oxidation with 30% H_2O_2 as in 4) was carried out in glacial AcOH on (IV), (V), (XIV), (XV), (XVI), and (XVII).

1,3,7,9-Tetrachlorophenothiazine 5-Dioxide (VI)—Colorless fine plates (from EtOH), m.p. 228~229°(decomp.). *Anal.* Calcd. for $C_{12}H_5O_2NCl_4S$: C, 38.99; H, 1.36; N, 3.79. Found : C, 38.61; H, 1.46; N, 4.01.

1,2,3,7,9-Pentachlorophenothiazine 5-Dioxide (XVIII)—Colorless platelets (from EtOH), m.p. 216~217°. *Anal.* Calcd. for $C_{12}H_4O_2NCl_5S$: C, 35.73; N, 1.00; N, 3.47. Found : C, 36.06; H, 1.10; N, 3.78.

1,3,4,7,9-Pentachlorophenothiazine 5-Dioxide (XIX)—Colorless platelets (from EtOH), m.p. 243~244°. *Anal.* Calcd. for $C_{12}H_4O_2NCl_5S$: C, 35.73; H, 1.00; N, 3.47. Found : C, 35.90; H, 1.06; N, 3.62.

Summary

It was found that some polychlorinated phenothiazines were prepared directly from the corresponding diphenylamines with thionyl chloride. This discovery was followed by investigations on the action of other sulfur compounds, such as thionyl bromide or sulfuryl chloride, but these two products merely acted as halogenating reagents and only some polybromo- or polychloro-diphenylamines were obtained from them.

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