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 C₁₃H₂₆O₃Cl₂S·H₂O:
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 C₃₃H₆₀O₆N₄Cl₂S·H₂O:
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% H₂O₂, the solution was refluxed for 2 hrs.,
the solvent was evaporated, and 30 cc. of water and also a little of MnO₂ 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 CHCl₃), m.p. 204~205° (decomp.). Anal. Calcd. for C₃₃H₆₀O₆N₄Cl₂S:
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-chloro-
phenothiazine 5-dioxide, which was easily synthesized via 2-chloro-10-acetylpheno-
thiazine.

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

(Research Laboratory, Shionogi & Co., Ltd.**)

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 phenothi-
zines.† 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).§

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

\[ \text{C}_{13}\text{H}_{15}\text{N} + 6 \text{SOCl}_2 \rightarrow \text{C}_{13}\text{H}_{21}\text{NCl}_4\text{S} + 3 \text{SO}_2 + 6 \text{HCl} \]

The sulfoxide derivative (V) of (IV) had m.p. 220~222° (decomp.)* 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'—

* Part I. This Bulletin, 5, 389(1957).
** 192 Imafuku, Amagasaki, Hyogo-ken (加納目出村, 岸本 学).
hexabromodiphenylamine (VII), m.p. 222~223°.\textsuperscript{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°.\textsuperscript{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

\textsuperscript{4)} Elson, et al.: \textit{Ibid.}, 1929, 1085.
\textsuperscript{5)} Chapman: \textit{Ibid.}, 1929, 571.
orientation of meta-substituted diphenylamines in thionation and determined that (IX) gave 2- and 4-chlorophenothiazines (X and XI). 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 relatively 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.

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**Experimental**

1) **General Procedure of Ring Closure and Chlorination with SOCl₂**—Ten volumes of SOCl₂ 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 SO₂ 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°. Colors purple with H₂SO₄. Anal. Calcd. for C₁₅H₁₃NCl₄S : 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 H₂SO₄. Anal. Calcd. for C₁₅H₁₃NCl₅S : C, 38.80; H, 1.09; N, 3.77. Found : C, 38.83; H, 1.21; N, 4.06.


2) **Bromination with SOBr₂**—Twenty volumes of SOBr₂ was added to one volume of diphenylamine.

After the initial violent reaction ceased, the mixture was warmed slightly to eliminate the excess of HBr-Br₂, poured on crushed ice, the precipitate was collected, and dried. The yellow crude product crystallised from CHCl₃.

2,4,6,2',4',6'-Hexabromodiphenylamine (VII)—Colorless plates, m.p. 222–223°. Analytical. Calcd. for C₁₅H₁₂Br₈: 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°. Analytical. Calcd. for C₁₅H₁₁Br₈Cl: C, 21.28; H, 0.60; N, 2.07. Found: C, 21.17; H, 0.72; N, 2.25.

3) Chlorination with SO₂Cl₂—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°. Analytical. Calcd. for C₁₅H₆Cl₈: 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°. Analytical. Calcd. for C₁₅H₈Cl₉: 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), (IV), (V), (X), (XI), (XIV), or (XV), was dissolved in a large amount of EtOH and reacted with 1 mole of 30% H₂O₂ 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°. Analytical. Calcd. for C₁₅H₂ONClS: 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°. Analytical. Calcd. for C₁₅H₂OCl₅S: 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°. Analytical. Calcd. for C₁₅H₂OCl₅S: 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% H₂O₂ as in 4) was carried out in glacial AcOH on (IV), (V), (XIV), (XV), (XVI), and (XVII).

1,3,4,7,9-Tetrachlorophenothiazine 5-Dioxide (XVIII)—Colorless fine plates (from EtOH), m.p. 223–229°. Analytical. Calcd. for C₁₅H₂O₂Cl₅S: 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°. Analytical. Calcd. for C₁₅H₂O₂Cl₅S: C, 35.73; H, 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°. Analytical. Calcd. for C₁₅H₂O₂Cl₅S: 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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