

## Phenothiazine Derivatives. VI<sup>1)</sup>. Reactions of Some Substituted Phenothiazines with Thionyl Chloride

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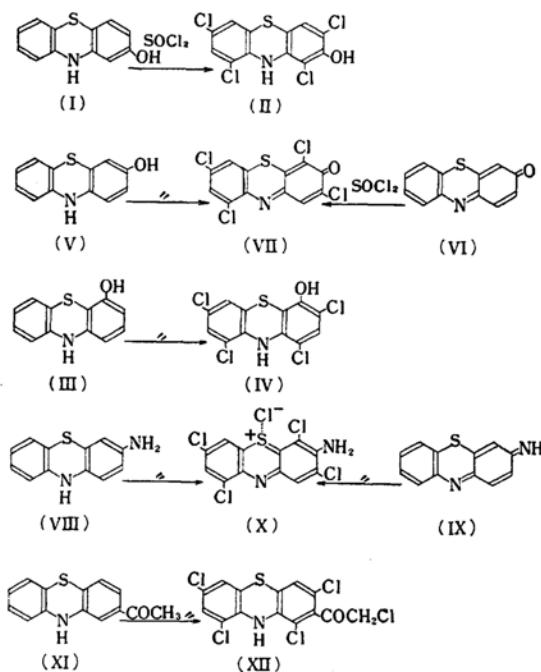
In Part II<sup>2)</sup> of the present series, it was reported that thionyl chloride transforms phenothiazine and its 5-oxide into 1,3,7,9-tetrachlorophenothiazine. Besides the present series, two reports have been published on the nuclear substitutions of phenothiazine derivatives with thionyl chloride. Namely, phenothiazine-1-carboxylic acid gave 3,7,9-trichlorophenothiazine-1-carbonyl chloride<sup>3)</sup>, and phenothiazine-2-carboxylic acid 1,3,7,9-tetra-

chlorophenothiazine-2-carbonyl chloride<sup>4)</sup>.

The present paper describes similar substitution reactions of some other phenothiazine derivatives with thionyl chloride.

**Mono-substituted Phenothiazines.**—As shown in Chart I, the action of thionyl chloride gave 1,3,7,9-tetrachloro-2-hydroxyphenothiazine (II) from 2-hydroxyphenothiazine (I), 2,4,7,9-tetrachloro-3-phenothiazine (VII) from 3-hydroxyphenothiazine (V) and from 3-phenothiazine (VI), and 3-amino-2,4,7,9-tetrachlorophenazathionium chloride (X) from 3-aminophenothiazine (VIII) and from 3-phenothiazine (IX). These three products, II, VII and X, had been obtained by the action of thionyl chloride on 3-hydroxydiphenylamine, 4-hydroxydiphenylamine and 4-aminodiphenylamine, respectively<sup>5)</sup>. In Part III<sup>6)</sup> of this series it was observed that the reaction of thionyl chloride with diphenylamine to form 1,3,7,9-tetrachlorophenothiazine proceeds through the intermediate formation of phenazathionium chloride and subsequent chlorination. The fact that the substituted phenothiazines and the corresponding diphenylamines gave the same products by the action of thionyl chloride affords support to the above mechanism of the reaction of thionyl chloride with diphenylamine. Thionyl chloride and 4-hydroxyphenothiazine (III) gave a new tetrachloro-4-hydroxyphenothiazine. As it is expected that the hydroxyl group in position 4 of 4-hydroxyphenothiazine will strengthen the 1,3-orienting effect by the imino group, the

CHART I



1) Part V: This Bulletin, 32, 371 (1959).

2) *Pharm. Bull. (Japan)*, 5, 393 (1957).

3) N. V. Savitskaya and M. N. Shahukina, *Zhur. Obshchei Khim.*, 24, 152 (1954).

4) A. Burger and J. B. Clements, *J. Org. Chem.*, 19, 1113 (1954).

5) This Bulletin, 32, 298 (1959).

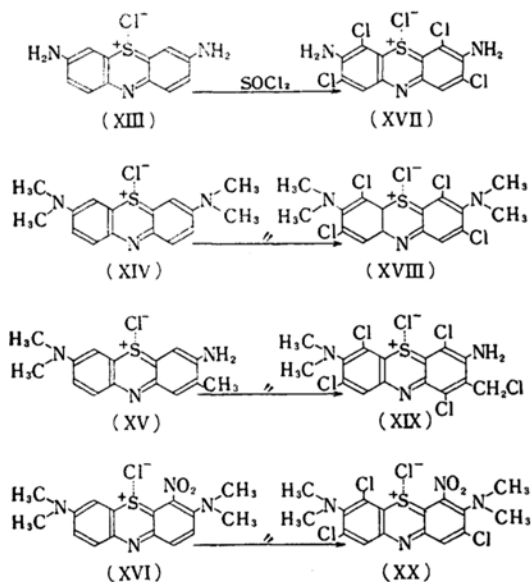
6) *Ibid.*, 32, 294 (1959).

product is assumed with great certainty to be 1,3,7,9-tetrachloro-4-hydroxyphenothiazine (IV).

2-Acetylphenothiazine (XI) gave a pentachloro derivative. A part of the chlorine atoms was found labile giving easily the chloride anion, and thus was present in the side chain. The positions of the chlorine atoms in the ring with the chlorinated acetyl group can not be presumed unequivocally, because the orienting effect by the acetyl group and that by the imino group do not fall on the same positions, but the product can be assumed to be 1,3,7,9-tetrachloro-2-(chloroacetyl)-phenothiazine (XII) in analogy to 1,3,7,9-tetrachlorophenothiazine-2-carboxylic chloride from phenothiazine-2-carboxylic acid<sup>(4)</sup>.

**Phenothiazine Dyes<sup>(7)</sup>.**—From among many known phenothiazine dyes, thionine (XIII), methylene blue (XIV), toluidine blue (XV) and methylene green B (XVI) were chosen for the reactions with thionyl chloride.

CHART II



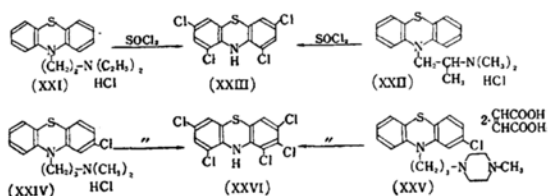
In the order of mention, they gave 3,7-diamino-2,4,6,8-tetrachlorophenazathionium chloride (XVII), 3,7-bis(dimethylamino)-2,4,6,8-tetrachlorophenazathionium chloride (XVIII), 3-amino-1,4,6,8-tetrachloro-2-(chloromethyl)-7-(dimethylamino)-phenazathionium chloride (XIX), and 2,6,8-trichloro-3,7-bis(dimethylamino)-4-nitrophenazathionium chloride (XX), respectively.

7) These dyes are expediently expressed in phenazathionium formulae.

As it is reasonably expected that the amino group and the dimethylamino group in positions 3 and 7 are stronger in the orienting effect than the competing nitrogen atom of position 10, substitution took place presumably in all the positions 2, 4, 6 and 8, unless already substituted. Toluidine blue (XV) gave a pentachloro derivative. It can be assumed by the same reason as stated above that three of the five chlorine atoms are situated at positions 4, 6, and 8. As substitution in position 1 is favored by both the nitrogen atom of position 10 and the methyl group in position 2, one is probably in position 1, and the remaining one in the methyl group to make chloromethyl group. Thus the pentachloro product is considered 3-amino-1,4,6,8-tetrachloro-2-(chloromethyl)-7-(dimethylamino)phenazathionium chloride (XIX).

**Phenothiazine Drugs.**—Four of the most important phenothiazine drugs were treated with thionyl chloride with results shown in Chart III. The same 1,3,7,9-tetrachlorophenothiazine (XXIII)<sup>2)</sup> was obtained from either diethazine (XXI) (2987 R.P.) or promethazine (XXII) (3389 R.P.). In a similar manner, 1,2,3,7,9-pentachlorophenothiazine<sup>2)</sup> (XXVI) was derived from chlorpromazine (XXIV) (4560 R.P.) and from prochlorperazine

CHART III



(XXV) (6140 R.P.). As the yields were nearly quantitative, the reaction with thionyl chloride may be useful to the qualitative and quantitative analyses of various phenothiazine drugs.

### Experimental

**General Procedure of Treatment with Thionyl Chloride.**—Thionyl chloride (10 ml.) was added dropwise to 1.0 g. of the compound to be treated, and the mixture was heated gently under reflux for 30 min., when hydrogen chloride and sulfur dioxide were evolved. The cooled mixture was poured onto crushed ice, and the product was collected, dried, and recrystallized.

**1,3,7,9-Tetrachloro-2-hydroxyphenothiazine (II) from 2-Hydroxyphenothiazine (I).**—Fine powder of chocolate color from chloroform-ethanol, m.p. 202~203°C (decomp.). Yield,

93%. The substance was identified with an authentic sample<sup>2)</sup>.

**1, 3, 7, 9-Tetrachloro-4-hydroxyphenothiazine (IV) from 4-Hydroxyphenothiazine (III).**—Fine powder with chocolate color from benzene, m.p. 168~170°C. Yield, 94%. The product IV gives bluish-violet color with sulfuric acid.

*Anal.* Found: C, 40.67; H, 1.10; N, 4.01. Calcd. for  $C_{12}H_5ONCl_4S$ : C, 40.82; H, 1.43; N, 3.97%.

**2, 4, 7, 9-Tetrachloro-3-phenothiazone (VII) from 3-Hydroxyphenothiazine (V) and from 3-Phenothiazone (VI).**—Fine crystals with pinkish tinge from ethanol-benzene, m.p. 145~146°C. Yields, 92% from V and 97% from VI. The product VII gives cobalt-blue coloration with sulfuric acid. The substance showed no depression of the melting point on admixture with an authentic sample<sup>2)</sup>.

**3-Amino-2, 4, 7, 9-tetrachlorophenazathionium Chloride (X) from 3-Aminophenothiazine (VIII) and from 3-Phenothiazine (IX).**—Reddish-violet fine powder from chloroform, m.p. 185~186°C. Yields, 89% from VIII and 99% from IX. The substance showed no depression of the melting point on admixture with an authentic sample<sup>2)</sup>.

**1, 3, 7, 9-Tetrachloro-2-(chloroacetyl)phenothiazine (XII) from 2-Acetylphenothiazine (XI).**—Green powder, m.p. 145~146°C. Yield, quantitative. Coloration with sulfuric acid is violet. Silver chloride was precipitated on adding silver nitrate to an alcoholic solution of the substance XII.

*Anal.* Found: C, 37.19; H, 1.93; N, 3.15. Calcd. for  $C_{14}H_6ONCl_5S \cdot 2H_2O$ : C, 37.37; H, 2.24; N, 3.11%.

**3, 7-Diamino-2, 4, 6, 8-tetrachlorophenazathionium Chloride (XVII) from Thionine (XIII).**—Bluish-purple fine powder from methanol, m.p. over 360°C. Yield, 99%. The substance gives dark green color with sulfuric acid.

*Anal.* Found: C, 35.99; H, 1.83; N, 10.54. Calcd. for  $C_{12}H_6N_3Cl_5S$ : C, 35.90; H, 1.51; N, 10.47%.

**2, 4, 6, 8-Tetrachloro-3, 7-bis(dimethylamino)phenazathionium Chloride (XVIII) from Methylene Blue (XIV).**—Greenish-blue fine crystals, m.p. over 360°C. Yield, 94%. The substance gives green color with sulfuric acid. When recrystallized from a mixture of dimethylformamide and water, it was transformed into the corresponding phenazathionium hydroxide, which was analyzed.

*Anal.* Found: C, 43.66; H, 3.28; N, 10.06. Calcd. for  $C_{16}H_{13}ON_3Cl_4S$ : C, 43.75; H, 3.44; N, 9.57%.

**3-Amino-1, 4, 6, 8-tetrachloro-2-(chloromethyl)-7-(dimethylamino)phenazathionium Chloride (XIX) from Toluidine Blue (XV).**—Purplish-blue fine powder from acetic acid, m.p. over 360°C. Yield, 96%. It gives reddish-brown color with sulfuric acid.

*Anal.* Found: C, 37.90; H, 2.72; N, 8.48. Calcd. for  $C_{15}H_{11}N_3Cl_4S$ : C, 37.68; H, 2.32; N, 8.79%.

**2, 6, 8-Trichloro-3, 7-bis(dimethylamino)-4-nitrophenazathionium Chloride (XX) from Methylene Green B (XVI).**—Green fine powder from methanol, m.p. 234~237°C (decomp.). Yield, quantitative. Coloration with sulfuric acid is violet.

*Anal.* Found: C, 40.88; H, 3.40; N, 12.09. Calcd. for  $C_{16}H_{14}O_2N_4Cl_3S$ : C, 41.05; H, 3.01; N, 11.97%.

**1, 3, 7, 9-Tetrachlorophenothiazine (XXI) from Diethazine (XIX) and from Promethazine (XX).**—Yellow needles from benzene, m.p. 234~235°C. Yields, 99% from XIX and 96% from XX. It was identified with an authentic sample<sup>2)</sup>.

**1, 2, 3, 7, 9-Pentachlorophenothiazine (XXVI) from Chlorpromazine (XXIV) and from Prochlorperazine (XXV).**—Faint-yellow or colorless needles from benzene, m.p. 204~205°C. Yields, 96% from XXIV and 90% from XXV. It was identified with an authentic sample<sup>2)</sup>.

## Summary

Some phenothiazine derivatives including dyes and drugs were treated with thionyl chloride and five new polychlorinated products and six known were obtained.

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