Phenothiazine Derivatives. VII[1]. *Reactions of Phenothiazines with Sulfuryl Chloride and with Chlorosulfonic Acid*

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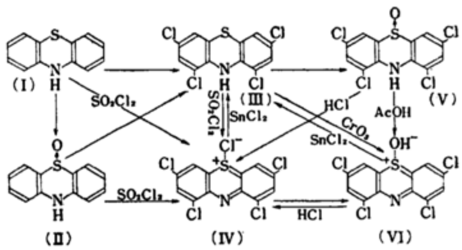
(Received October 9, 1958)

In the previous papers of this series, reactions of diphenylamines and phenothiazines with thionyl halides, and of diphenylamine with sulfuryl chloride were described[2]. The present paper deals with the reactions of phenothiazines with sulfuryl chloride and with chlorosulfonic acid.

CHART I



The action of sulfuryl chloride on phenothiazine (I), on phenothiazine 5-oxide (II), and on 1,3,7,9-tetrachlorophenothiazine (III) produced chocolate-colored mixtures which, on treatment with water, gave a highly chlorinated product. The molecular weight of the purified product was found to be 309, and it was analyzed as $C_{12}H_5ONCl_4S$, corresponding to 1,3,7,9-tetrachlorophenazathionium hydroxide (VI).

Brady and Smiles[3] obtained 1,3,7,9-tetrachlorophenazathionium hydroxide(VI) by treating 1,3,7,9-tetrachlorophenothiazine 5-oxide (V) with aqueous sulfuric acid, and they described the substance as a brownish-red powder, decomposing somewhat gradually at 200°C and giving a purple solution in sulfuric acid. The substance obtained by the present author is a fine powder of chocolate color melting at 210~211°C (decomp.) and giving violet coloration with sulfuric acid. We may well be justified in regarding the present substance as identical with the substance of Brady and Smiles.

Without treatment with water, 1,3,7,9-tetrachlorophenazathionium chloride (IV) was obtained as the precursor of the hydroxide VI. Hydrolysis of the purified chloride IV with aqueous sulfuric acid or with ethanolic potassium hydroxide gave the phenazathionium hydroxide VI. Therefore, it was concluded that the treatment of the primary reaction mixtures with water caused a hydrolysis by sulfuric acid which was generated from water and the remaining sulfuryl chloride.

Mutual transformations of the four 1,3,7,9-tetrachlorophenothiazine derivatives, III, IV, V and VI, were further investigated. Reduction of 1,3,7,9-tetrachlorophenathionium chloride (IV) and of the hydroxide VI with stannous chloride gave 1,3,7,9-tetrachlorophenothiazine (III), while the hydroxide VI was produced either by oxidation of the phenothiazine III with chromic anhydride in benzene or by intramolecular rearrangement of 1,3,7,9-tetrachlorophenothiazine 5-oxide (V) in acetic acid. Action of dry hydrogen chloride on the 5-oxide (V) and on the phenazathionium hydroxide VI yielded the phenazathionium chloride IV. These transformations demonstrate that the four chlorine atoms are situated at the corresponding positions in the four compounds concerned. The infrared absorptions of

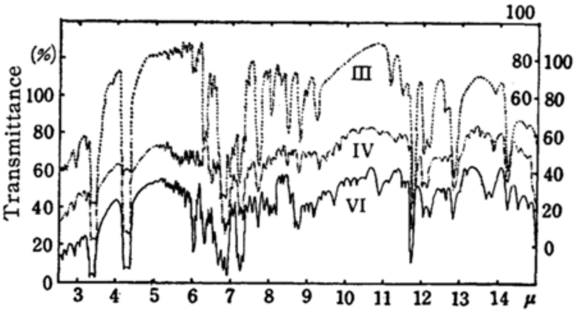


Fig. 1. Infrared spectra in Nujol of 1,3,7,9-tetrachlorophenothiazine (III), 1,3,7,9-tetrachlorophenazathionium chloride (IV), and the hydroxide VI.

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[1] Part VI, This Bulletin, **32**, 480 (1959).

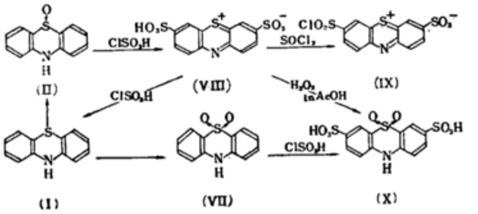
[2] Part II, *Pharm. Bull.* (*Japan*), **5**, 395 (1957); Part III, IV and VI, This Bulletin, **32**, 294, 296, 480 (1959).

[3] O. L. Brady and S. Smiles, *J. Chem. Soc.*, **97**, 1562 (1910).

three (III, IV and VI) of the four compounds also indicate that they are similarly substituted (Fig. 1).

Phenothiazine 5,5-dioxide (VII) did not react with sulfuryl chloride, but chlorosulfonic acid transformed it into a disulfonic acid, probably 3,7-disulfophenothiazine 5,5-dioxide (X), as shown in Chart II.

CHART II



The action of chlorosulfonic acid on phenothiazine (I) and on its 5-oxide (II) gave an inner salt VIII of 3,7-disulfophenazathionium hydroxide. The inner salt VIII has converted into the disulfonic acid X by oxidation with 30% hydrogen peroxide in acetic acid, and into the inner salt IX of 3-sulfo-7-(chlorosulfonyl)phenazathionium hydroxide on treatment with thionyl chloride. Thus the sulfo groups and the chlorosulfonyl group in these inner salts are situated at the same positions as in the disulfophenothiazine 5,5-dioxide (X), which were assumed to be 3 and 7 as mentioned above.

Experimental

Reduction of 1,3,7,9-Tetrachlorophenazathionium Chloride (IV) and of 1,3,7,9-Tetrachlorophenazathionium Hydroxide (VI) with Stannous Chloride.—a) A mixture of 1.0 g. of 1,3,7,9-tetrachlorophenazathionium chloride (IV), described below, and 0.8 g. of stannous chloride was dissolved in 20 ml. of acetic acid, and then 1.0 g. of 35% hydrochloric acid was added. The solution was refluxed during 3 hr., and the cooled mass was poured into water. The yellow precipitate was collected, dried, and recrystallized from dioxane. Yellow needles, m. p. 235~236°C. Yield, 96%. The substance was identified with 1,3,7,9-tetrachlorophenothiazine (III) by a mixed melting point determination with an authentic sample[2].

b) Similarly, 1,3,7,9-tetrachlorophenazathionium hydroxide (VI), described below, gave the same tetrachlorophenothiazine (III) in a yield of 94%.

1,3,7,9-Tetrachlorophenazathionium Chloride (IV).—a) Sulfuryl chloride (10 ml.) was added to 1.0 g. of phenothiazine (I), and the mixture was gently refluxed for 30 min. Then the excess of sulfuryl chloride was evaporated under reduced pressure. The product was recrystallized from benzene. 1,3,7,9-Tetrachlorophenazathionium chloride (IV) was obtained in chocolate-colored needles, m. p. 223~224°C (decomp.). Yield, nearly quantitative. It gives purple coloration with sulfuric acid.

Anal. Found: C, 38.95; H, 1.43; N, 3.98. Calcd. for $C_{12}H_4NCl_5S$: C, 38.79; H, 1.09; N, 3.77%.

On treatment with sulfuryl chloride in a similar manner, phenothiazine 5-oxide (II) and 1,3,7,9-tetrachlorophenothiazine (III) gave the same product IV also in nearly quantitative yields.

b) A carbon tetrachloride solution of 1,3,7,9-tetrachlorophenothiazine 5-oxide (V) was saturated with dry hydrogen chloride, the chocolate-colored solution was refluxed for 1 hr., and then the solvent was distilled off. The residue was recrystallized from benzene. 1,3,7,9-Tetrachlorophenazathionium chloride (IV) was obtained quantitatively.

1,3,7,9-Tetrachlorophenazathionium Hydroxide (VI).—a) The reaction mixture resulting from phenothiazine (I) and sulfuryl chloride as described above, was poured into water, and the chocolate-colored product was collected, dried and recrystallized from benzene. 1,3,7,9-Tetrachlorophenazathionium hydroxide (VI) was obtained in chocolate-colored needles, m. p. 210~211°C. Yield, quantitative. It gives violet coloration with sulfuric acid.

Anal. Found: C, 40.49; H, 1.54; N, 4.03; mol. wt. (Rast), 309. Calcd. for $C_{12}H_5ONCl_4S$: C, 40.82; H, 1.43; N, 3.97%; mol. wt., 353.

b) 1,3,7,9-Tetrachlorophenazathionium chloride (IV) (0.2 g.) was dissolved in 5 ml. of sulfuric acid, and then the mixture was poured into 50 ml. of water. A nearly quantitative yield of the same hydroxide VI was obtained.

c) The chloride IV (0.2 g.) was dissolved in 50 ml. of hot ethanol, and a solution of 0.1 g. of potassium hydroxide in 5 ml. of hot ethanol was added. After reflux during 1 hr., the solvent was distilled off, and then the residue was neutralized with 10% hydrochloric acid. Recrystallization of the insoluble part from benzene gave 1,3,7,9-tetrachlorophenazathionium hydroxide (VI).

d) To a solution of 1.0 g. of 1,3,7,9-tetrachlorophenothiazine (III) in 50 ml. of benzene, 1.0 g. of chromic anhydride was added little by little. The mixture was refluxed on a water bath during 3 hr. The solvent was distilled off, and the residue was poured onto crushed ice. The same hydroxide VI was obtained in a quantitative yield.

e) A solution of 1.0 g. of 1,3,7,9-tetrachlorophenothiazine 5-oxide (V) in 30 ml. of acetic acid was refluxed for 1 hr., and the chocolate-colored solution was evaporated in vacuo. The residue was recrystallized from benzene, and 1,3,7,9-tetrachlorophenazathionium hydroxide (VI) was obtained in chocolate-colored fine needles.

Inner Salt VIII of 3,7-Disulfophenazathionium Hydroxide.—Chlorosulfonic acid (10 ml.) was added dropwise to phenothiazine (I), and the mixture was heated gently under reflux for 30 min., and then the cooled mass was poured onto crushed ice. The precipitate was collected, dried, and recrystallized from benzene. The inner salt VIII of 3,7-disulfophenazathionium hydroxide was obtained in dark reddish-violet powder, m.p. 225~226°C. Yield, 93%. It gives bluish-violet coloration with sulfuric acid.

Anal. Found: C, 36.56; H, 2.39; N, 3.85. Calcd. for $C_{12}H_7O_6NS_3 \cdot 2H_2O$: C, 36.64; H, 2.82; N, 3.56%.

Treatment of phenothiazine 5-oxide (II) with chlorosulfonic acid in a similar manner gave the same product in a yield of 97%.

Inner Salt IX of 3-Sulfo-7-(chlorosulfonyl)phenazathionium Hydroxide.—Thionyl chloride (10 ml.) was added drop by drop to 1.0 g. of the inner salt VIII of 3,7-disulfophenazathionium hydroxide, when hydrogen chloride and sulfur dioxide was evolved. After reflux during 30 min., the mixture was poured into water. The precipitate was collected, dried, and recrystallized from ethyl acetate. The inner salt IX of 3-sulfo-7-(chlorosulfonyl)phenazathionium hydroxide was obtained in dark-violet powder, m.p. 163~164°C. Yield, 0.9 g. (94%). It gives cobalt-blue coloration with sulfuric acid.

Anal. Found: C, 38.70; H, 1.80; N, 3.66. Calcd. for $C_{12}H_6O_5NClS_3$: C, 38.35; H, 1.61; N, 3.73%.

3,7-Disulfophenothiazine 5,5-Dioxide (X).—a) The reaction of phenothiazine 5,5-dioxide (VII) and sulfuryl chloride gave 3,7-disulfophenothiazine 5,5-dioxide (X) as a hygroscopic, dark-green substance. Yield, over 86% of the theory. The substance X is soluble in water, in ethanol, and in methanol. The sodium, potassium, calcium and barium salts are easily soluble in water. Coloration with sulfuric acid is reddish-purple.

b) To a solution of substance VIII in 40 ml. of acetic acid, 1.0 ml. of 30% hydrogen peroxide was added, and the solution was heated on a water bath during 3 hr. Evaporation of the solvent gave the same disulfonic acid X. Yield of the crude product, quantitative.

Summary

Reactions of some phenothiazines with sulfuryl chloride and with chlorosulfonic acid were investigated. With sulfuryl chloride, phenothiazine (I), its 5-oxide (II), and 1,3,7,9-tetrachlorophenothiazine (III) gave the same product, 1,3,7,9-tetrachlorophenazathionium chloride (IV), which yielded the corresponding hydroxide VI by the action of aqueous sulfuric acid and of ethanolic potassium hydroxide. To establish the structural relationship of these substances, mutual transformations were carried out. Treatment of phenothiazine and of its 5-oxide with chlorosulfonic acid gave the inner salt VIII of 3,7-disulfophenazathionium hydroxide, which yielded the inner salt IX of 3-sulfo-7-(chlorosulfonyl)phenazathionium hydroxide by the action of thionyl chloride. Chlorosulfonic acid converted phenothiazine 5,5-dioxide into 3,7-disulfophenothiazine 5,5-dioxide which was obtained also by the oxidation of the inner salt VIII with 30% hydrogen peroxide in acetic acid.

The author expresses his thanks to Professor Y. Urushibara, the University of Tokyo, for his helpful guidance throughout this work, to Dr. K. Takeda, Director of the Laboratory, for his permission to conduct this research, and also to the members of the Center of Microanalytical Services, Shionogi and Co., Ltd., for the elementary analyses and the infrared spectal measurements.

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