viscous oily residue was immediately dissolved in glacial AcOH and warmed on a water bath for 2 hrs. Excess of AcOH was removed under reduced pressure and the residue was recrystallized from EtOH or hydr. EtOH. Yield, 70~80%.

b) Reaction of 80% Formic Acid with (III): A mixture of 0.005 mole of (III) and 6 cc. of 80% formic acid was heated in an oil bath for 5 hrs. at 110~120°. After removal of excess formic acid under pressure, crystalline residue was collected and recrystallized from EtOH. These compounds were undepressed on admixture with the compounds prepared by the above a) method.

Summary

2-R-5-R′-*s*-Triazolo[3,4-*b*]-1,3,4-thiadiazoles (V) were synthesized starting with 2-hydrazino-5-R-1,3,4-thiadiazole (III : R=CH_3, C_2H_5, *n*-C_3H_7, *iso*-C_4H_9, C_6H_5), reacting them with either ethyl orthoacylate or ethyl acylimidate (R′=H, CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9) to form ethyl N′-(5-R-1,3,4-thiadiazol-2-yl)hydrazonoacylate (IV), and cyclization with acetic acid. Treatment of (III) by heating with 80% formic acid produced 2-R-*s*-triazolo-[3,4-*b*]-1,3,4-thiadiazole (V, R′=H).

(Received April 2, 1957)

UDC 547.869.2

66. Hideo Kano and Manabu Fujimoto: Phenothiazine Derivatives. I. Synthesis of Sulfoxide and Sulfone Homologs of Chlorpromazine.

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Chlorpromazine was shown to be very effective agent as a potent tranquilizer, antiemetic, analgesic, spasmolytic, neuroleptic, or ganglioplegic. Many workers have recently reported the formation *in vivo* and the elimination in urine of chlorpromazine sulfoxide after chlorpromazine administration.[1]

Therefore, we decided to prepare chemically further compounds of this type, e.g., chlorpromazine sulfone. The free base of chlorpromazine (II) has been usually prepared by the condensation of 2-chlorophenothiazine**(Ia)[2] and N,N-dimethyl-3-chloropropylamine in the presence of sodium amide.[3] The same pattern was repeated with N,N-dimethyl-3-chloropropylamine (DMCPA) and 2-chlorophenothiazine 5-oxide (IV) or 5-dioxide (IXa), obtained by the oxidation of (Ia) or 2-chloro-10-acetylphenothiazine (VIIa), but the yield of the free bases of chlorpromazine sulfoxide (V) and sulfone (X) was relatively low,[4] as shown in Chart 1.

Whereas the sulfoxide derivatives, (V) and (VI), could be prepared by the direct oxidation of (II) or (III), the sulfone analogs (X and XI) were derived only from sulfone-type phenothiazine (IX). In view of this, the synthesis of 2(or 4)-chlorophenothiazine 5-dioxide (IX) was attempted, although it was realized that 10-acylated phenothiazine might be suitable.

The physicochemical properties of (II), (V), (VI), (X), and (XI) are recorded in Table I and Figs. 1~4.

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** The nomenclature of phenothiazines conforms to the style of the Ring Index (1940).

1) N.P. Salzman, *et al.*: Nature, **176**, 1122(1955); Kopf: Klin. Wochschr., **15/16**, 455(1956); B. Kinberger, *et al.*: Svenska Läkart, **53**, (9) 501(1956).
2) French Pat. 1,029,987(1953).
3) French Pat. 1,075,117(1954).
4) cf. H. Gilman, J. Eisch: J. Am. Chem. Soc., **77**, 3862(1955).

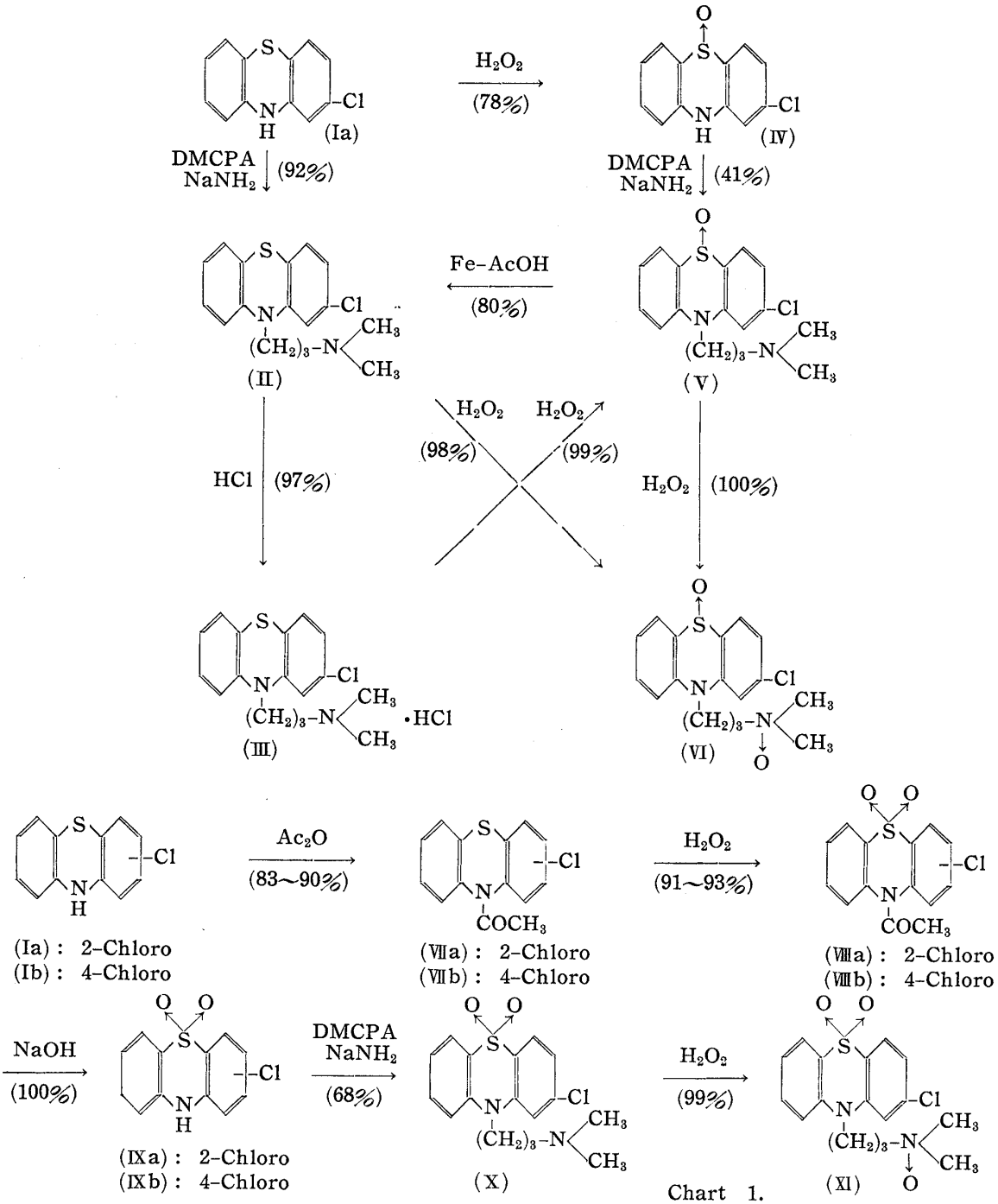
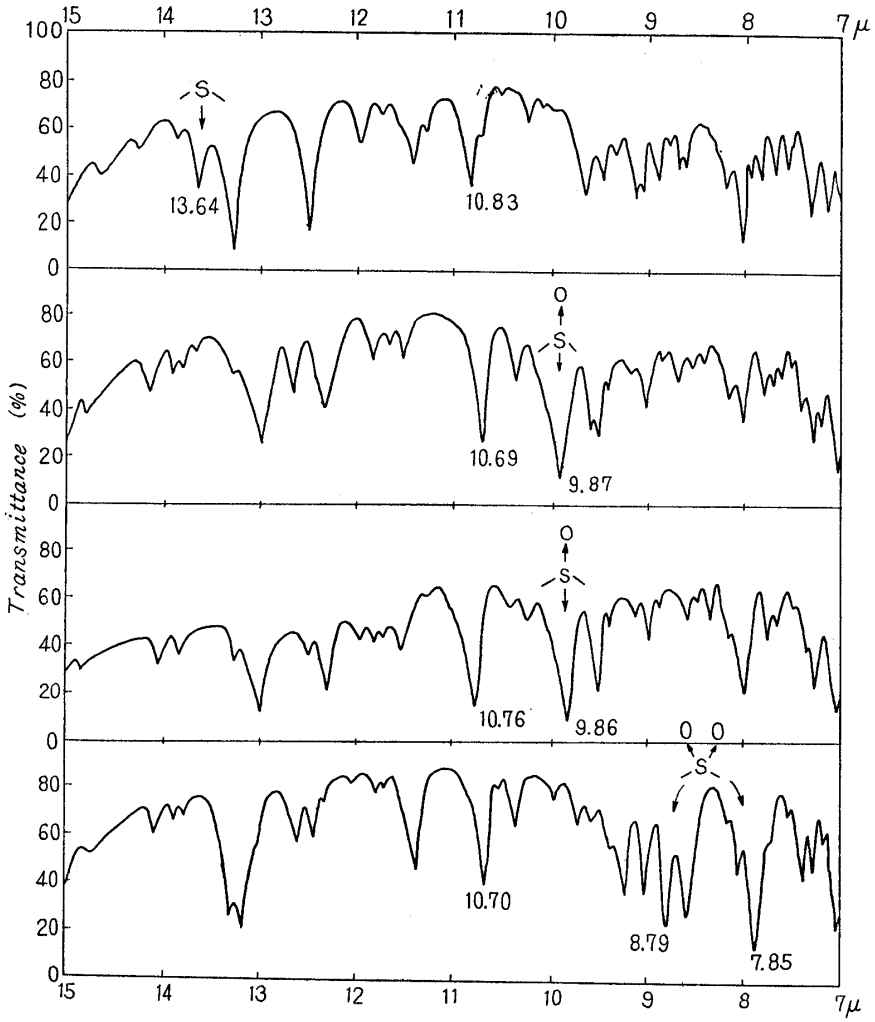


Chart 1.

TABLE I.

Product	m.p. (°C)	b.p. (°C/mm. Hg)	Color by H_2SO_4	I.R. λ_{max}^{nujol}	m.p. of salts (°C)	
(II)	58	216/4	Rose to red-violet	13.64 μ.	Hydrochloride[3](III) :	196
					Phenolphthalinate :	173
					Picrate[3] :	173
(V)	115	222/0.01	Brown-violet to red-violet (Sulfoxide)	9.87 μ.	Hydrochloride :	206
					Hydrogen maleate :	157
					Picrate[1] :	209
(VI)	105	—	Brown-black to red-violet (Sulfoxide)	9.86 μ.	Picrate :	187
(X)	118	275/4	Colorless (Sulfone)	7.85 μ.	Hydrochloride :	211
				8.79 μ.	Picrate :	239
(XI)	—	—	Colorless	—	Picrate :	205



Infrared Absorption Spectra (in Nujol)
(Perkin-Elmer single-beam spectrophotometer, Model 12 C)

All the oxidized derivatives of chlorpromazine formed colorless hydrochlorides, but often (without sulfone products) the salts tended to color from red to purple on exposure to air and sunlight. Moreover, none of these was as active and as curative as chlorpromazine itself. The more oxidized the compounds were, the less effective in clinical use.[5] The pharmacological data will be published elsewhere by our co-workers.

Thanks are expressed to Dr. K. Takeda, the Director of this Laboratory, for his help and encouragement during this investigation, to Mr. Matsui for his kind help in infrared spectral measurement, and also to the members of this Center of Microanalytical Service.

Experiemental

2-Chloro-10-(3-dimethylaminopropyl)phenothiazine (II) from its Sulfoxide (V)—(V) (5.0 g.) was dissolved in 50 cc. of glacial AcOH and 20 cc. of xylene, and to this hot solution, iron powder (1.0 g.) was added with agitation. The whole suspension was refluxed for 16 hrs. After cooling, the inorganic residue was filtered off and the filtrate was evaporated under a reduced pressure. The residue was treated with NaOH solution, extracted with benzene, concentrated as usual, and the residue was rectified *in vacuo*, b.p_4 210~218°. The light yellow oil solidified as light yellow plates, m.p. 58°. Yield, 3.8 g.(80%). The phenolphthalinate, m.p. 196°, and the picrate, m.p. 177°, showed no depression of m.p. on admixture with the corresponding samples from (Ia).

2-Chlorophenothiazine 5-Oxide (IV)—70 cc. of 30% H_2O_2 was added to a solution of 2-chloropheno-

5) cf. N. P. Salzmann, B. B. Brodie : J. Pharm. Exptl. Therap., **118**, 46(1956).

thiazine (Ia) (50.0 g.) in 1 L. of EtOH with stirring. The solution was refluxed for 4 hrs. and the initial yellow color changed rapidly to reddish violet. EtOH was evaporated, the precipitate was collected, washed with EtOH, and the crude product (52.8 g.) was recrystallized from dimethylformamide-dioxane, giving colorless fine crystals, m.p. 262~264°(decomp.). The yield of pure product was 41.6 g.(78%). I.R. λ_{max}^{Nujol} : 10.09 μ (sulfoxide). (IV) is insoluble in water and in usual organic solvents. *Anal.* Calcd. for $C_{12}H_8ONClS$: C, 57.69; H, 3.65; N, 5.98. Found : C, 57.73, H, 3.23; N, 5.61.

2-Chloro-10-(3-dimethylaminopropyl)phenothiazine 5-Oxide (V)—i) A suspension of 12.1 g. of (IV), 2.4 g. of $NaNH_2$ powder, and 200 cc. of xylene was refluxed at 160° for 4 hrs. To the resulting mixture 5% xylene solution of DMCPA was added during 2 hrs. and refluxed for the next 24 hrs. After cooling, water and 10% HCl were added until the pH was 3 and the precipitate (IV) was filtered off. The decanted organic layer was reëxtracted twice with water, and the whole aqueous layer was alkalized and extracted with benzene. The benzene extract, dried over Na_2SO_4, was evaporated and its residue distilled *in vacuo*, $b.p_{0.01}$ 219~222°. Yield, 6.7 g.(41%). Colorless crystals, m.p. 114~115°(from AcOEt).

Hydrochloride : Colorless prisms (from acetone), m.p. 204~206°. *Anal.* Calcd. for $C_{17}H_{20}ON_2Cl_2S$: C, 54.49; H, 5.48; N, 7.51. Found : C, 54.98; H, 5.43; N, 7.55.

Picrate : Yellow needles, m.p. 207~209°. *Anal.* Calcd. for $C_{23}H_{22}O_8N_5ClS$: C, 48.82; H, 4.14; N. 12.29. Found : C, 49.07; H, 3.94; N, 12.44.

Hydrogen maleate, m.p. 157~158°.

ii) To 15.0 g. of chlorpromazine[3](III) in 100 cc. of EtOH 4.6 cc. of 30% H_2O_2 was added with stirring. The solution was refluxed for 5 hrs., the solvent was removed, and the pinkish residue was recrystallized from acetone to colorless plates, m.p. 204~206°, which was identified as the hydrochloride of (V). Yield, 15.5 g.(99%).

2-Chloro-10-(3-dimethylaminopropyl-N-oxido)phenothiazine 5-Oxide (VI)—i) By the same oxidation with 2 moles of 30% H_2O_2, (II) gave colorless prisms (from acetone), m.p. 104~105°. Yield 98%. *Anal.* Calcd. for $C_{17}H_{19}O_2N_2ClS \cdot H_2O$: C, 55.36; H, 5.74; N, 7.60. Found : C, 55.10; H, 6.25; N, 7.54. This free base of (VI) was soluble in water and the hydrochloride was hygroscopic.

Picrate : m.p. 185~187°. *Anal.* Calcd. for $C_{23}H_{22}O_9N_5ClS \cdot \frac{1}{2}H_2O$: C, 46.99; H, 3.94; N, 11.89. Found : C, 46.82; H, 4.02; N, 12.20.

ii) From the free base of (V) to (VI), the yield of oxidation product was quantitative.

2-Chloro-10-acetylphenothiazine (VIIa)—100 cc. of Ac_2O was added to 23.4 g. of 2-chlorophenothiazine (Ia), m.p. 198°,[2] and the mixture was refluxed for 1 hr. From the light yellow solution obtained, AcOH-Ac_2O was distilled off and the residue was rectified at 235~238° at 4 mm. Hg. The yellow oil (22.8 g.; 83%) slowly solidified to yellow plates (from $CHCl_3$), m.p. 78~80°. *Anal.* Calcd. for $C_{14}H_{10}ONClS$: C, 60.98; H, 3.66; N, 5.08. Found : C, 60.79; H, 3.68; N, 5.53.

4-Chloro-10-acetylphenothiazine (VIIb)—From 4-chlorophenothiazine (Ib), m.p. 118°,[2] (VIIb) was obtained as colorless plates (from $CHCl_3$), m.p. 219~220°. Yield, 90%. *Anal.* Calcd. for $C_{14}H_{10}ONClS$: C, 60.98; H, 3.66; N, 5.08. Found : C, 60.83; H, 3.81; N, 5.08.

2-Chloro-10-acetylphenothiazine 5-Dioxide (VIIIa)—To a solution of 22.8 g. of (VIIa) in AcOH (150 cc.), 20 cc. of 30% H_2O_2 was added, and the mixture was heated to 90° during 4 hrs. The light pinkish white crystals were collected. The filtrate was concentrated and poured into a large volume of cold water. The whole product was recrystallised from benzene. The yield of colorless needles (m.p. 208~209°) was 23.2 g.(91%). *Anal.* Calcd. for $C_{14}H_{10}O_3NClS$: C, 54.64; H, 3.28; N, 4.55. Found: C, 54.64; H, 3.39; N, 4.57.

4-Chloro-10-acetylphenothiazine 5-Dioxide (VIIIb)—From (VIIb), (VIIIb) was obtained as colorless plates (from $CHCl_3$), m.p. 260~261°(decomp.). Yield, 93%. *Anal.* Calcd. for $C_{14}H_{10}O_3NClS$: C, 54.64; H, 3.28; N, 4.55. Found : C, 54.87; H, 3.58; N, 4.69.

2-Chlorophenothiazine 5-Dioxide (IX)—A mixture of 19.0 g. of (VIIIa), 130 cc. of EtOH, and NaOH, solution (4.0 g. in 15 cc. of water) was refluxed for 2 hrs. After the removal of EtOH, 300 cc. of water was added, crude product was collected, washed, and dried. Yield, 16.4 g.(100%). Colorless platelets (from dehyd. EtOH), m.p. 276~277°. I.R. λ_{max}^{Nujol} : 7.84, 8.80 μ (sulfone). *Anal.* Calcd. for $C_{12}H_8O_2NClS$: C, 54.26; H, 3.03; N, 5.27. Found : C, 54.38; H, 3.06, N, 5.44.

4-Chlorophenothiazine 5-Dioxide (IXb)—Colorless plates (from acetone), m.p. 283~284°. Yield, almost quantitative. I.R. λ_{max}^{Nujol} : 7.89, 8.77 μ (sulfone). *Anal.* Calcd. for $C_{12}H_8O_2NClS$: C, 54.26; H, 3.03; N, 5.27. Found : C, 53.95; H, 3.41; N, 5.47.

2-Chloro-10-(3-dimethylaminopropyl)phenothiazine 5-Dioxide (X)—6.0 g. of (IXa), 1.2 g. of finely powdered $NaNH_2$, and 200 cc. of dioxane were mixed with agitation and then refluxed for 2 hrs. in an oil bath of 140° to complete the generation of NH_3. To this, 17 cc. of 19.8% toluene solution of DMCPA was added drop by drop and the mixture was refluxed for 8 hrs. Insoluble matter was filtered off, the solvent was removed, and the yellow oily product, $b.p_4$ 270~275°, solidified to colorless needles (from EtOH), m.p. 116~118°. Yield, 5.4 g.(68%). *Anal.* Calcd. for $C_{17}H_{19}O_2N_2ClS$: C, 58.18;

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.

(Received May 11, 1957)

UDC 547.869.2

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 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′-

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

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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).