Bromination of 10-Phenylphenothiazine and 10-Phenylphenoxazine

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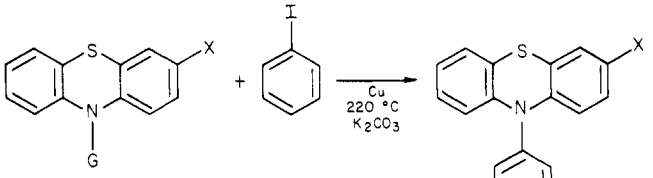
The reaction of either 10-phenylphenothiazine (1) with bromine in acetic acid or the cation radical of 1 with bromide ion gives ring substitution only and in accord with customary stoichiometry for nucleophilic substitution of aromatic cation radicals. However, the reaction of 1 with pyridinium bromide perbromide (2) gives predominantly 10-phenyl ring substitution and a small amount of ring substitution products. Evidence is presented which indicates that ring substitution occurs via cation radical whereas 10-phenyl substitution proceeds via electrophilic attack on the neutral molecule 1. Substitution of 10-phenylphenoxazine (4) occurs predominantly but not exclusively on the phenoxazine ring; some bromination does occur on the 10-phenyl ring. In contrast, the reaction of 4 with bromine gives only ring mono- and disubstitution products. These results indicate that both 1 and 4 react similarly under the same conditions.

We have observed that the reaction of 10-phenylphenothiazine (1) with pyridinium bromide perbromide (2) in acetic acid gave 10-(*p*-bromophenyl)phenothiazine (3) in good yields (60–65%).[1] The reaction mixture was not analyzed for other brominated products. In contrast, Shine and co-workers[2] have reported that the reaction of either 10-phenylphenoxazine (4) with bromine in acetic acid or the radical cation of 4 with bromide ion gives phenothiazine ring substitution *only* and in accord with the customary stoichiometry for nucleophilic substitution of aromatic cation radicals. That is, 3-bromo-10-phenylphenoxazine (5), 3,7-dibromo-10-phenylphenoxazine (6), and compound 4 were obtained. They made a careful search for 10-(*p*-bromophenyl)phenoxazine (7) in their reactions but found none. Therefore, we reinvestigated the bromination of 1 under several reaction conditions and studied the reaction of phenoxazine 4 with pyridinium bromide perbromide (2) to determine if our previous findings could be reconciled with those of Shine.

Results and Discussion

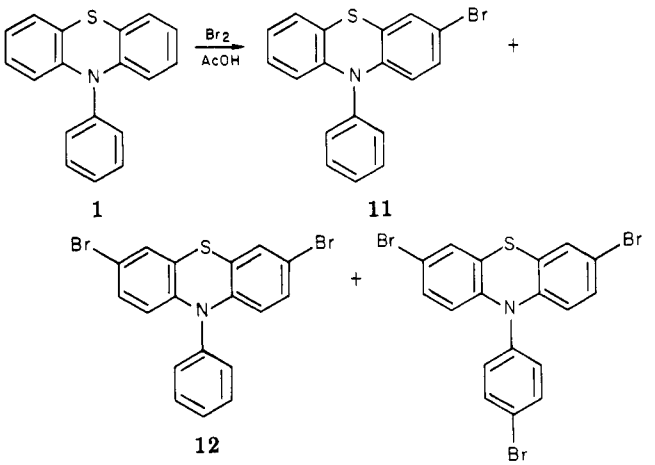
The structures of brominated products were unambiguously assigned by the comparison of their ^{13}C NMR spectra with those of authentic samples. These were prepared by Ullmann coupling of the appropriate phenothiazine and haloaromatic compounds.



8, G = X = H
9, G = H; X = Br

1, X = H
11, X = Br

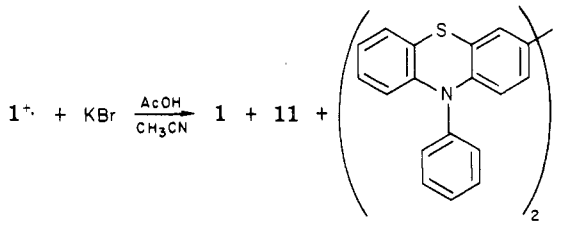
The bromination of 1 with bromine in acetic acid yielded 3-bromo-10-phenylphenothiazine (11) (56%) and 3,7-dibromo-10-phenylphenothiazine (12) (20%). Only a small amount (2%) of 3,4′,7-tribromo-10-phenylphenothiazine (13) was obtained from this reaction and *no* 10-(*p*-bromophenyl)phenothiazine (3) was isolated. This product distribution was similar to that observed by Shine in the reaction of 10-phenylphenoxazinium cation radical ($4^{+\cdot}$) with bromine and suggested that bromination of 1 proceeded via the cation radical of 1. Accordingly, the cation



1 11

12 13

radical $1^{+\cdot}$ was generated by treating 1 with perchloric acid



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and subsequently reacted with bromide ion to give 3-bromo compound 11 (43%), reduced starting material, 1 (42%), and a trace amount of 3,3′-bis-10,10′-diphenylphenothiazine dimer (14); again the 4′-bromo product 3 was not detected.

Thus, the bromination of 1 with bromine in acetic acid appears to involve initial oxidation of 1 to its cation radical $1^{+\cdot}$, which undergoes subsequent nucleophilic substitution in the same manner as described for $4^{+\cdot}$. Reactions of this kind have been characterized kineticly[3] and essentially follow the sequence of steps listed in Scheme I. Also, the

Scheme I

$$1H + {}^1/_2Br_2 \rightleftarrows 1H^{+\cdot} + Br^-$$

$$1H^{+\cdot} + Br^- \rightarrow (1H/Br)\cdot$$

$$(1H/Br)\cdot + 1H^{+\cdot} \rightarrow (1H/Br)^+ + 1H$$

$$(1H/Br)^+ + Br^- \rightarrow 11 + HBr$$

(1) Biehl, E. R.; Shine, H. J., private communications.
(2) Shine, H. J.; Wu, S. M. *J. Org. Chem.* **1979**, *44*, 3310.
(3) Bard, J. A.; Ledwith, A.; Shine, H. J. *Adv. Phys. Org. Chem.* **1976**, *13*, 155.

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reaction mixture of 1 with bromine in acetic acid did turn initially to the characteristic wine-red color of $1^{+}\cdot$.

Since the half-wave oxidation potential of $1^{+}\cdot$ and $11^{+}\cdot$ are within 0.06 V, **(1H/Br)·** can also be oxidized by $11^{+}\cdot$ (Scheme II). This alternate disproportionation pathway

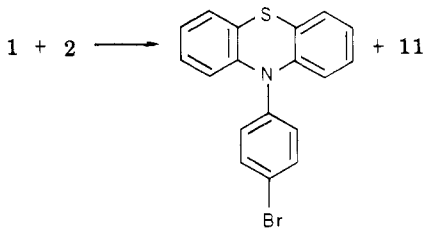
Scheme II

$$1^{+}\cdot + 11 \rightleftharpoons 1 + 11^{+}\cdot$$

$$\mathbf{(1H/Br)}\cdot + 11^{+}\cdot \rightarrow \mathbf{(1H/Br)}^{+} + 11$$

has been pointed out by previous investigators.[3,4]

However, the bromination of 1 with 1.1 equiv of pyridinium bromide perbromide (2) gave the 4′-bromo product 3 in a yield of 63% and the 3′-bromo isomer 11 in only 27%



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yield. No dimeric products of phenothiazine 1 were detected which indicates that a substantial portion of bromine substitution, especially that on the 10-phenyl group, may be electrophilic. Apparently, the use of the mild brominating and oxidizing reagent 2 allows electrophilic substitution of 1 to compete successfully with aromatic substitution on its cation radical $1^{+}\cdot$. However, bromination of 1 using bromine in acetic acid proceeds most likely by the latter mechanism. The possibility exists in which substitution with bromide ion is, in fact, electrophilic, occuring after electron exchange between cation radical and nucleophile (Scheme III). If that mechanism were

Scheme III

$$21\mathbf{H}^{+}\cdot + 2Br^{-} \rightarrow 21\mathbf{H} + Br_2$$

$$1\mathbf{H} + Br_2 \rightarrow \mathbf{3} \text{ or } 11 + HBr$$

operative in either of the bromination reactions involving $1^{+}\cdot$ electrophilic bromine substitution on the 10-phenyl group would have been expected. However, such substitution was not observed in those reactions which indicates they do not proceed via the electron exchange mechanism.

Geometric requirements appear to determine which bromination reaction pathway predominantly occurs. Construction of a Drieding model of $1^{+}\cdot$ indicates that $H_{1(9)}$–$H_{2'(6')}$ peri interactions force the aryl ring out of the plane of the central ring containing the nitrogen atom and sulfur atom (Figure 1). Thus, resonance interactions between N_{10} and the 10-phenyl ring would be hindered sterically.

ESR and UV–vis spectroscopy data support the above conclusion. The ESR spectrum of $1^{+}\cdot$, which has been reported by Clarke and co-workers,[6] reveals that ortho and meta proton splittings are very much larger than the para splitting in the 10-phenyl ring. This behavior indicates that the phenyl ring's π-system is decoupled from that of the remainder of the radical, so that spin density can no

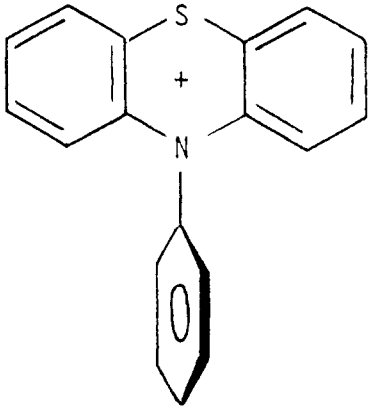

Figure 1. Structure of radical cation of 1.

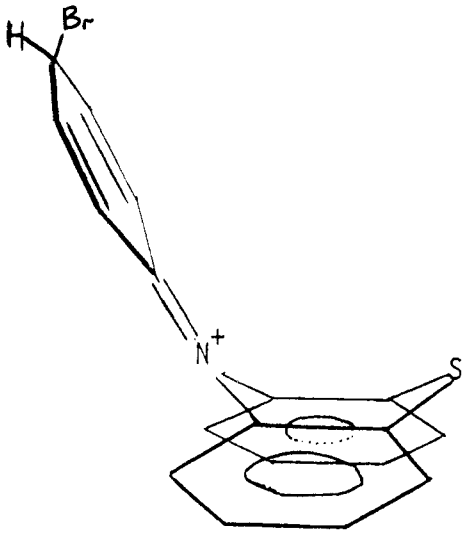

Figure 2. Important resonance contributing structure for electrophilic pathway.

longer be transmitted effectively to the remote para position. Good agreement was obtained between calculated and experimental splittings when they assumed that the plane of the phenyl ring in the 10-position is twisted ca. 70° from the plane of the remainder of the radical.

Visible absorption data[7] also indicate the lack of electronic interaction between the 10-phenyl and phenothiazine ring systems in $1^{+}\cdot$. For example, the absorption maxima of cation radicals of 10-alkyl- and 10-arylphenothiazines are in the same range (510–515 nm). This is also true for their respective dications which are in the range of 457–460 nm. That nucleophilic substitution of cation radical $1^{+}\cdot$ occurs only on the phenothiazine portion of the molecule most likely reflects the greater stability of the radical in **(1H/Br)·** located on the phenothiazine ring as compared to that located on the 10-phenyl ring.

However, the construction of a Drieding model shows that the lone pair of electrons on N_{10} in the "butterfly" structures of 1 are delocalized more readily onto the 10-phenyl group than onto the phenothiazine portion of the molecule. Figure 2 represents an important contributor for the electrophilic pathway. In a sense, the 10-phenyl substituent serves as a mechanistic probe for monitoring electrophilic substitution in these systems.

The X-ray structure of 2′-methoxy-10-phenylphenothiazine (15) shows that the 10-phenyl ring is perpendicular to the plane of the central ring containing the nitrogen and

(4) Shine, H. J.; Silber, J. J.; Bussey, R. J.; Okuyama, T. *J. Org. Chem.* **1972**, *37*, 2691.
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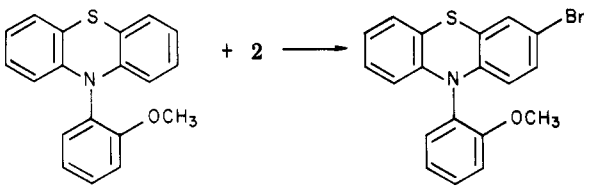
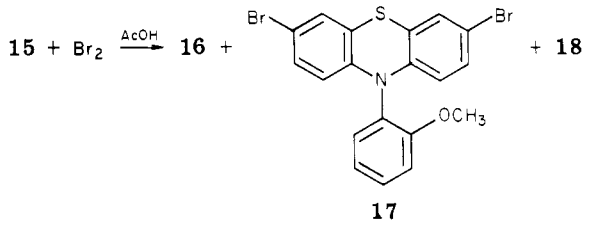


15 16

sulfur atoms.[8] Therefore, bromination of **15** via the electrophilic pathway should be retarded. The reaction of **15** with pyridinium bromide perbromide (**2**) was carried out, yielding, in support of our argument, only 2′-methoxy-3-bromo-10-phenylphenothiazine (**16**). The absence of bromination of the 10-phenyl ring substituted with the moderately activating methoxy group indicates that bromination of the phenothiazine ring proceeds predominantly via the cation radical of **15**.

Bromination of **15** in acetic acid gave compound **16** (50%) as well as 2′-methoxy-3,7-dibromo-10-phenylphenothiazine (**17**) (13%) and a small amount (1.5%) of



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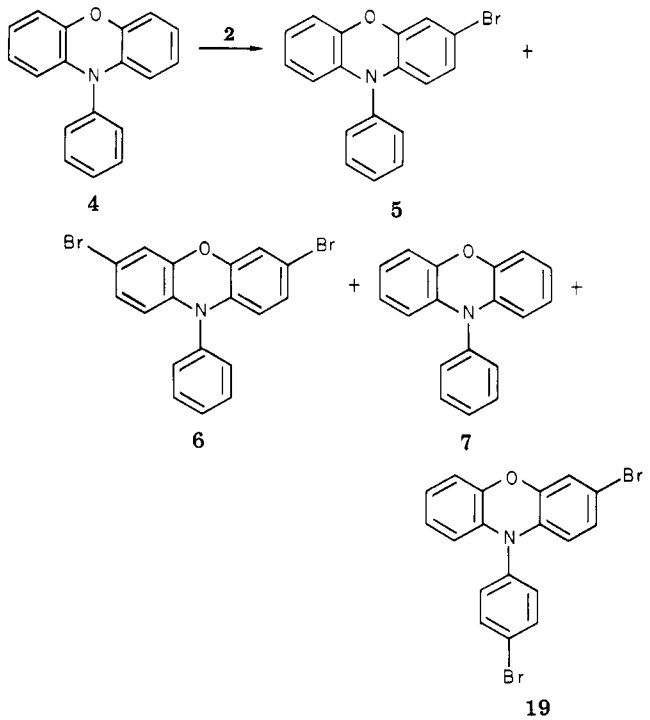
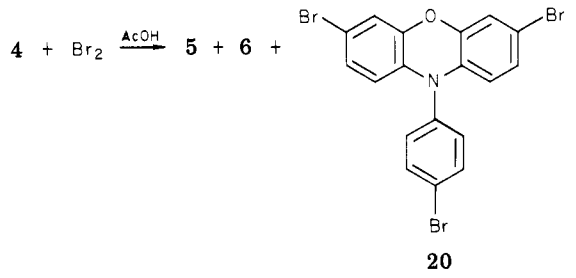
2′-hydroxy-3′,5′,3,7-tetrabromo-10-phenylphenothiazine (**18**). Here too, the bulky 2′-methoxy group effectively twists the 10-aryl ring out of the plane of the phenothiazine nucleus and blocks the N_{10} activation of the 10-phenyl ring which, in turn, prevents the bromination at $C_{4'}$.

Finally, 10-phenylphenoxazine (**4**) was brominated with perbromide **2** to give two products analogous to those observed in the reaction of **1** with **2**: 10-(*p*-bromophenyl)phenoxazine (**7**) (10%) and 3-bromo-10-phenylphenoxazine (**5**) (19%) plus 3,4′-dibromo-10-phenylphenoxazine (**19**) (3%) and 3,7-dibromo-10-phenylphenoxazine (**6**) (11%). The formation of **7** and **19** indicates that bromination of **4** with pyridinium bromide perbromide also is, in part, electrophilic. However, the amount of bromination which occurs on the phenothiazine portion of the molecule with **2** is greater than that on the 10-phenyl ring which is in contrast to the reaction of **1** with **2**. Dielectric relaxation measurements indicate that when oxygen replaces sulfur in folded molecules such as phenothiazine the resultant molecule is more nearly planar.[10] Thus, the 10-phenyl ring in **4** would be expected to be twisted from the plane of the remainder of the molecule in order for the latter to achieve a more nearly planar structure. Therefore, the electrophilic substitution on 10-phenyl in **4** would be retarded for the same reason as suggested for the reaction of **2** with the 2′-methoxy compound **15**, that is, steric inhibition of resonance between the lone pair on N_{10} and the 10-phenyl group.



4 5 6 7 19

We repeated the reaction of **4** with bromine in acetic acid and obtained, in addition to those reported by Shine,[2] a small amount of 3,4′,7-tribromo-10-phenylphenoxazine (**20**) (5%). Thus, our bromination results and those of Shine



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are now reconciled; both compounds (**1** and **4**) react similarily with bromine in acetic acid or with pyridinium bromide perbromide.

Experimental Section

Melting points are uncorrected. Carbon-13 nuclear magnetic resonance (^{13}C) were recorded on a Bruker WP200SY spectrometer. Chemical shifts are reported in parts per million downfield from Me_4Si and splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Mass spectra (electron impact, 70 eV) were determined on a duPont Dymaspec 321 GC/MS. Preparative chromatography was performed by using E. M. Merck silica gel 60 PF-254 and column chromatography was done by using 70–230 mesh silica gel 60 or aluminum oxide 90 (E. M. Merck).

Materials. 10-Phenylphenothiazine was on hand from a previous study[10] and phenoxazine was made by a literature method of Gilman.[11] 10-Phenylphenoxazine was prepared by the reaction of phenoxazine and bromobenzene as described by Shine and Wu.[2] All other materials were available commercially and were purified by either distillation or recrystallization prior to use.

Bromination of 10-Phenylphenothiazine (1) with Br_2 in Acetic Acid. A stirred solution of **1** (1.0 mmol, 275 mg) in acetic acid (25 mL) was flushed with nitrogen for 5 min, then bromine (0.06 mL, 1.1 mmol) was added dropwise, and stirring was continued for 8 h. The solution turned pink immediately, then changed gradually to deep red, next to green, and finally to black with the evolution of hydrogen bromide. The solvent was evaporated in vacuo to yield a black powdery material which was redissolved in aqueous sodium bicarbonate (10 mL). The resulting mixture was extracted with five 20-mL portions of benzene. The orange extracts were combined, dried over anhydrous Na_2SO_4, filtered and evaporated to yield an oily material; TLC indicated the presence of 3 components. This oil was chromatographed on

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(9) Koga, Y.; Takahashi, H.; Higasi, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3359.
(10) Biehl, E. R.; Chiou, H.; Reeves, P. C. *J. Heterocycl. Chem.* **1976**, *13*, 77.
(11) Gilman, H.; Moore, L. O. *J. Am. Chem. Soc.* **1957**, *79*, 3485.

silica gel using benzene as the eluent. The first compound to be eluted off the column was 3-bromo-10-phenylphenothiazine (**11**) (198.2 mg, 56%): mp 97–98 °C; mass spectrum (70 ev), d, m/e 355 ($M^+ + 2$), and m/e 353 (M^+) of equal intensity; ^{13}C NMR 117.1 (C_1), 127.0 (C_2), 122.4 (C_3), 129.4 (C_4), 114.4 (C_{4a}), 119.3 (C_{5a}), 128.3 (C_6), 122.7 (C_7), 126.7 (C_8), 116.1 (C_9), 140.7 (C_{9a}), 143.4 (C_{10a}), 143.8 ($C_{1'}$), 130.7 ($C_{2'(6')}$), 130.8 ($C_{3'(5')}$), 128.7 ($C_{4'}$). Anal. Calcd for $C_{18}H_{12}BrNS$: C, 61.02; H, 3.42; N, 3.95. Found: C, 61.08; H, 3.25; N, 3.90. The next compound to be eluted was 3,7-dibromo-10-phenylphenothiazine (**12**): 86.6 mg (20%); mp 157–158 °C; mass spectrum (70 ev), t, m/e 435 ($M^+ + 4$), m/e 433 ($M^+ + 2$), and m/e 431 (M^+), relative intensities ca. 1:2:1, respectively; ^{13}C NMR: 117.1 ($C_{1(9)}$), 128.7 ($C_{2(8)}$), 123.0 ($C_{3(7)}$), 134.0 ($C_{4(6)}$), 114.6 ($C_{4a(5a)}$), 140.1 ($C_{9a(10a)}$), 142.9 ($C_{1'}$), 130.5 ($C_{2'(6')}$), 130.9 ($C_{3'(5')}$), 126.8 ($C_{4'}$). The last compound to be eluted was 3,4′,7-tribromo-10-phenylphenothiazine (**13**): 10.7 mg (2%); mp 177–178 °C; mass spectrum (70 ev), q, m/e 515 ($M^+ + 6$), 513 ($M^+ + 4$), 511 ($M^+ + 2$), and 509 (M^+), relative intensities 1:3:3:1, respectively; ^{13}C NMR 117.3 ($C_{1(9)}$), 132.1 ($C_{2(8)}$), 122.0 ($C_{3(7)}$), 134.3 ($C_{4(6)}$), 115.2 ($C_{4a(5a)}$), 139.4 ($C_{9a(10a)}$), 142.6 ($C_{1'}$), 129.0 ($C_{2'(6')}$), 129.7 ($C_{3'(5')}$), 122.5 ($C_{4'}$). Compounds **11**–**13** were identified further by comparison of their physical and spectral properties with those of authentic samples prepared by the Ullman reaction described below.

Reaction of 1 with Pyridinium Bromide Perbromide. To a solution of **1** (275 mg, 1.0 mmol) in 15 mL of dichloromethane and 10 mL of freshly distilled acetonitrile was added 263 mg (1.1 mmol) of pyridinium bromide perbromide (**2**) in portions over a period of 20 min. The reaction mixture was worked up in the same manner described above for the bromination of **1** with bromine to yield a brown organic residue which was separated into two fractions by chromatography on a silica gel with a petroleum ether–CH_2Cl_2. Compound **11** was the first one to be eluted (32 mg, 9% yield). The later fraction consisted of a mixture of two components which were separated by thick-layer chromatography on silica gel plates using hexane as eluent to yield an additional 63.7 mg of **11** (combined yield of 27%) and 10-(*p*-bromophenyl)phenothiazine (**3**): 216 mg (61%); mp 132–133 °C after recrystallization from petroleum ether and a trace of acetone; mass spectrum (70 ev), d, m/e 355 ($M^+ + 2$) and 353 (M^+) of equal intensities; ^{13}C NMR 116.7 ($C_{1(9)}$), 126.9 ($C_{2(8)}$), 122.9 ($C_{3(7)}$), 126.9 ($C_{4(6)}$), 121.4 ($C_{4a(5a)}$), 143.7 ($C_{9a(10a)}$), 140.5 ($C_{1'}$), 133.8 ($C_{2'(6')}$), 131.7 ($C_{3'(5')}$), 121.4 ($C_{4'}$). Anal. Calcd for $C_{18}H_{12}BrNS$: C, 61.02; H, 3.42; N, 3.95. Found: C, 61.05; H, 3.45; N, 3.89. The structure of **3** was also assigned on the basis of comparison of its spectral and physical data with those of an authentic sample prepared by an Ullman synthesis described below.

Reaction of 10-Phenylphenothiazinium Perchlorate ($1^{+}\cdot$) with Bromide Ion. To a well-stirred mixture of potassium bromide (262.6 mg, 2.2 mmol) and 30 mL of acetonitrile (flushed with nitrogen for 15 min) was added 374 mg (1.0 mmol) of $1^{+}\cdot$ and the resulting mixture stirred 8 h at room temperature. After the evaporation of the solvent, the residue was purified by chromatography on a long silica gel column (50 mL, 1.0 cm od) and eluted with hexane to yield 152.2 mg (43%) of **11**. Further elution with 95:5/petroleum ether–benzene gave 115.5 mg (42%) of **1** and, finally, elution with 90:10/petroleum ether–CH_2Cl_2 gave 2.5 mg of a white fluffy material **14**, mp 221–222 °C, which appears to be a dimer of **1** on the basis of its mass spectrum (m/e 548).

Ullman Synthesis of Authentic Samples. As a typical example, the preparation of 10-(*p*-bromophenyl)phenothiazine (**3**) is described. A mixture of 423 mg (2.14 mmol) of phenothiazine (**8**), 536 mg (2.27 mmol) of *p*-dibromobenzene (**10**), 304 mg (2.2 mmol) of potassium carbonate, and 424 mg of activated Cu powder was refluxed for 48 h at 220-230 °C. Upon cooling the tarry residue was extracted with 3 × 20 mL of dichloromethane, and combined extracts were passed quickly through a charcoal plug and then a short column of deactivated alumina (8 mL, 1.0 cm od). The solvent was removed in vacuo and the residue was recrystallized from hexane to give **3** (483 mg, 63.8% yield), mp 131–133 °C. This material was identical in all respects with the one isolated from the reaction of 10-phenylphenothiazine with perbromide **2**.

Bromination of 10-Phenylphenoxazine (4) with Br_2 in Acetic Acid. Using the same conditions as those described for the reaction of **1** with bromine, 259 mg (1.0 mmol) of **4** and 0.06 mL (1.1 mmol) of Br_2 were converted to 3-bromo-10-phenylphenoxazine (**5**) (118 mg (35%), mp 89–90 °C (lit.[2] 90–92 °C)), 3,7-dibromo-10-phenylphenoxazine (**6**) (54.3 mg (13%), mp 143–144 °C (lit.[2] mp 142–144 °C)), and 3,4′,7-tribromo-10-phenylphenoxazine (**20**) (24.8 mg (5%), mp 170–171 °C).

Reaction of 4 with Pyridinium Bromide Perbromide (2). Using the same procedure as that described for the reaction of **1** with **2** the following bromo compounds were isolated and identified: 62.9 mg (19%) of **5**, 46.3 mg (11.1%) of **6**, and 32.1 mg (9.5%) of 10-(*p*-bromophenyl)phenoxazine (**7**), mp 198–200 °C (lit.[2] 199–200.5 °C).

Reaction of 2′-Methoxy-10-phenylphenothiazine (15) with Br_2 in Acetic Acid. Using the same procedure described for the bromination of **1** with bromine in acetic acid, 305 mg (1.0 mmol) of **15** was treated with 0.06 mL (1.1 mmol) of bromine in 25 mL of acetic acid to yield 2′-methoxy-3-bromo-10-phenylphenothiazine (**16**) (192 mg, 50%): mp 133–135 °C; mass spectrum (70 ev), d, m/e 385 ($M^+ + 2$) and 383 (M^+) of equal intensities; also 2′-methoxy-3,7-dibromo-10-phenylphenothiazine (**17**) (60.2 mg, 13%) was obtained: mp 140–142 °C; mass spectrum (70 ev), t, m/e 465 ($M^+ + 4$), 463 ($M^+ + 2$), and 461 (M^+), relative intensities 1:2:1, respectively. In addition, a bright yellow solid (**18**) (9.1 mg, 1.5%) was also isolated, mp >300 °C. On the basis of its mass spectrum (four bromines) and NMR spectrum, we tentatively have assigned it the structure of 2′-hydroxy-3,7,3′,5′-tetrabromo-10-phenylphenothiazine.

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Registry No. **1**, 7152-42-3; $1^{+}\cdot$perchlorate salt, 52156-15-7; **3**, 63524-03-8; **4**, 37832-25-0; **5**, 71041-11-7; **6**, 71041-12-8; **7**, 71041-21-9; **8**, 92-84-2; **10**, 106-37-6; **11**, 89922-57-6; **12**, 89922-58-7; **13**, 89922-59-8; **14**, 89922-60-1; **15**, 60665-93-2; **16**, 89922-62-3; **17**, 89922-63-4; **18**, 89922-64-5; **20**, 89922-61-2; Br_2, 7726-95-6; KBr, 7758-02-3; pyridinium bromide perbromide, 39416-48-3.