Mechanistic Aspects of the Bromination of 10-Substituted Phenothiazines

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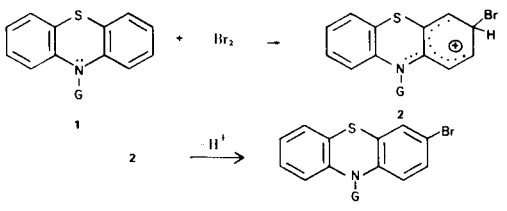
The addition of 1 and 2 molar equivalents of bromine to a series of 10-alkylphenothiazines, **1a-d** (methyl, ethyl, *n*-propyl, and isopropyl, respectively), yields the corresponding 3-bromo- and 3,7-dibromo-10-alkylphenothiazines (**11a-d** and **12a-d**, respectively). Evidence which supports the typical electrophilic aromatic substitution mechanism is presented. Radical cations (**12a-d**$^{\cdot+}$) are produced when **12a-d** are treated with 1 or 2 molar equivalents of bromine. Upon boiling in acetic acid these radical cations are converted predominantly to 1,3,7,9-tetrabromophenothiazine (**5**) and the parent 3,7-dibromo-10-alkylphenothiazine (**12a-d**) with the evolution of hydrogen bromide. The 10-methyl radical (**12a**$^{\cdot+}$) gives, in addition, 1,3,7-tribromo-10-methylphenothiazine (**15**). A mechanism if proposed for these reactions in which initial dealkylation of **12b-d**$^{\cdot+}$ to 3,7-dibromophenothiazine radical cation (**13**$^{\cdot+}$) occurs followed by reduction of **13**$^{\cdot+}$ by bromide ion to parent 3,7-dibromophenothiazine (**13**). Subsequent bromination of **13** by molecular bromine produced in the previous redox reaction yields 1,3,7-tribromo- (**14**) and 1,3,7,9-tetrabromo-(**5**) phenothiazines. The small size of the methyl group allows **12a** to be brominated at the 1-position prior to dealkylation. In addition to undergoing bromination at the 3- and 7-position, 10-isopropylphenothiazine (**1d**) is oxidized to the radical cation **12e**$^{\cdot+}$ when treated with bromine. 10-Benzylphenothiazine (**1e**), however, undergoes oxidation to radical cation **1e**$^{\cdot+}$ exclusively. This radical cation debenzylates readily at room temperature and is converted finally into phenothiazine.

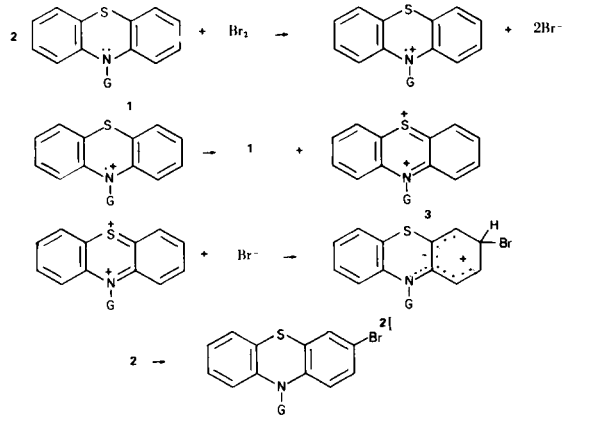
Three mechanisms are possible for the bromination of 10-substituted phenothiazines, **1**. The first path (Mechanism 1) is the typical electrophilic aromatic substitution mechanism in which the lone electron pair on nitrogen stabilizes by resonance the transition state leading to the cationic intermediate, **2**.



Mechanism 1

Alternatively, bromine, a good oxidizing agent, may initially oxidize **1** to radical cation **1**$^{\cdot+}$ which may be attacked directly by bromide ion at position 3 or **1**$^{\cdot+}$ may disproportionate (Mechanism 2) initially to dication **3** and **1**. Subsequent nucleophilic addition of bromide ion to the 3-position of **3** affords **2** which is the same intermediate obtained by the electrophilic mechanism.

Shine has suggested a similar disproportionation mechanism for the reaction of thianthrene radical cation with nucleophiles such as amino compounds (2), nitrite ion (3), pyridine (3), water (4), and electron rich benzene derivatives (5) on the basis of stoichiometry and kinetic data when experimentally obtainable (4,5).



Mechanism 2

The reaction of phenothiazine perchlorate with nitrite ion was observed by Shine and co-workers (3) to yield 3-nitrophenothiazine and phenothiazine in a stoichiometric relationship consistent with the disproportionation mechanism. However, no kinetic evidence was presented in that study to support the mechanism. Treatment of phenothiazine perchlorate with either chloride or bromide ions afforded both 3-halo- and 3,7-dihalophenothiazines which indicated that these reactions were not nucleophilic substitutions. It was suggested that the reaction of phenothiazine radical cation and chloride or bromide ion might involve electron exchange first, followed by halogenation by molecular halogen.

Parker and co-workers (6) have criticized Shine's disproportionation mechanism and have suggested another mechanism from which a third possibility for the mechanism of bromination can be derived.

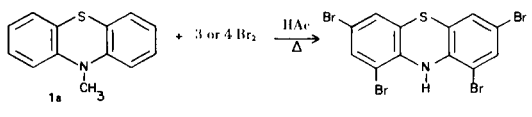
$$2\ \mathbf{1} + Br_2 \rightarrow 2\ \mathbf{1}^{\cdot+} + 2Br^-$$
$$\mathbf{1}^{\cdot+} + Br^- \rightarrow \mathbf{1}^{\cdot+}/Br^- \text{ (complex)}$$
$$\mathbf{1}^{\cdot+}/Br^- + \mathbf{1}^{\cdot+} \rightarrow \mathbf{1} + \text{1-Br}$$

Mechanism 3

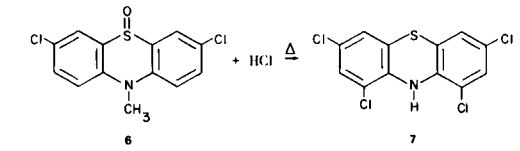
Although the mechanism of bromination of 10-alkylphenothiazines has not been extensively studied, the few reported studies (7,8) indicate that alkyl substituents influence greatly the path of the bromination reaction.

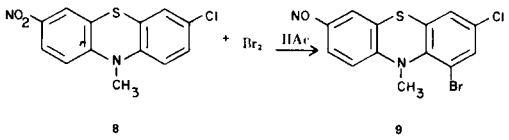
For example, the reaction of bromine (1 equivalent) with unsubstituted phenothiazine in acetic acid at room temperature gives phenazathionium perbromide, **4**. Nuclear bromination of **4** occurs in boiling acetic acid to give 3,7-dibromophenothiazine (**9**); a monobromo derivative cannot be obtained by this method. In contrast, bromination (bromine/acetic acid) of the 10-methyl compound, **1a**, proceeds smoothly at room temperature to yield 3-bromo-10-methyl-phenothiazines (**7**), albeit in very low yield. The use of the milder brominating agent, pyridinum hydrobromide perbromide, at 0° gives monobromo product in good yields (**8**).

Bromination of **1a** with either 3 or 4 equivalents of bromine, however, requires boiling in acetic acid and yields 1,3,7,9-tetrabromophenothiazine, **5**, the methyl group being removed. Schmalz and Burger (10) have also observed

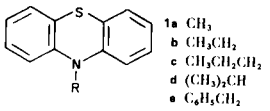


demethylation in the reductive halogenation of 3,7-dichloro-10-methylphenothiazine-5-oxide, **6**, with boiling concentrated hydrochloric acid which afforded 1,3,7,9-tetrachlorophenothiazine, **7**. In that study, demethylation was believed necessary to avoid unfavorable steric interactions between the 10-methyl group and the entering chlorine atom at positions 1 or 9. However, other nonsteric factors must be involved since Bodea *et al.* (11) have observed that the reaction of bromine with 3-nitro-7-chloro-10-methylphenothiazine, **8**, occurs without demethylation and yields the corresponding 1-bromo derivative, **9**.





Thus a study of the bromination and dealkylation of various 10-alkylphenothiazines, **1a-e**, in the presence of varying amounts of bromine in acetic acid was carried out in order to obtain more information on the role of the 10-substituent on the mechanism of these two reactions.



EXPERIMENTAL

Melting points were determined on a Fischer Johns apparatus and are uncorrected. Visible absorption spectra were measured in concentrated sulfuric acid on a Cary Model 118 Spectrophotometer; infrared absorption spectra were determined in potassium bromide pellets with a Perkin-Elmer Model 457 spectrophotometer. The nmr spectra were obtained with a Perkin-Elmer Model R12B spectrophotometer (TMS as internal reference).

Column chromatography utilized alumina (Alcoa F-20) and analytical grade solvents were used for elution; petroleum ether (b.p. 30-60°), benzene. Thin layer chromatography utilized commercially prepared thin layer chromatography plates (20 x 20 cm, silica gel containing a fluorescent indicator, Eastman, No. 6060). Fractions were spotted in carbon disulfide, eluted with benzene in petroleum ether (1:4), and individual spots were detected using uv light.

Materials.

10-Alkylphenothiazines (**1a-e**).

These compounds were available from a previous study (12).

Authentic Samples of Bromo-substituted 10-Alkylphenothiazines.

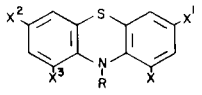
The 3-bromo and 3,7-dibromo derivatives, unless otherwise stated, were prepared by the addition of 1 and 2 equivalents of bromine, respectively, to a stirred solution of **1a-e** in glacial acetic acid at room temperature according to the procedure of Bodea (7).

3-Bromo-10-methylphenothiazine.

This compound was prepared by the low temperature bromination of **1a** using pyridinum hydrobromide perbromide (8). See

Table I

Nmr Spectra and R_f Values for Some Brominated Phenothiazine and 10-Alkylphenothiazines

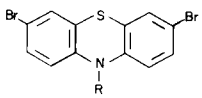


	R	X	X^1	X^2	X^3	Nmr Spectra	R_f (a)
13	H	H	3-Br	7-Br	H	Insoluble in all common nmr solvents	0.05
12a	CH_3	H	3-Br	7-Br	H	6H (m) τ 2.78 ~3.5 (aromatic); 3H (s) τ 6.70 (-N-CH_3)	0.50
12b	C_2H_5	H	3-Br	7-Br	H	6H (m) τ 2.78 ~3.53 (aromatic); 2H (q) τ 6.3 (-N-CH_2-); 3H (t) τ 8.67 (-CH_3)	0.58
12c	*n*-C_3H_7	H	3-Br	7-Br	H	6H (m) τ 2.79 ~3.54 (aromatic); 2H (t) τ 6.33 (-N-CH_2-); 2H (sex.) τ 8.25 (-CH_2-); 3H (t) τ 9.03 (-CH_3)	0.65
14	H	1-Br	3-Br	7-Br	H	6H (m) τ 2.72 ~3.68 (aromatic and -N-H)	0.54
15	CH_3	1-Br	3-Br	7-Br	H	Preparative sample of **15** contaminated with **14**. However, s (3H) 6.52 τ band assigned to N-CH_3.	0.76
5	H	1-Br	3-Br	7-Br	3-Br	Insoluble in all common nmr solvents	0.01

(a) Benzene and petroleum ether, 1:4.

Table II

The Reaction of 3,7-Dibromo-10-alkyl Phenothiazines with 1 or 2 Molar Equivalents of Bromine in Acetic Acid



Compound R	Molar Equivalent of Br_2	Non-Dealkylated Product Yield, % (1,3,7-tribromo-10-alkyl) (15)	Dealkylated Products Yield, % 13 (3,7-dibromo)	14 (1,3,7-tribromo-)	5 (1,3,7,9-tetrabromo)1	Recovery of Starting Material, %
12a-CH_3	1	10.6	---	1.5	50	51.3
12a-CH_2	2	17.6	---	1.6	52.2	28
12b-C_2H_5	1	---	trace	3.4	21.3	88.3
12b-C_2H_5	2	---	trace	2.8	35.1	69.1
12c-*n*-C_3H_7	1	---	trace	2.7	23.8	87.4
12c-*n*-C_3H_7	2	---	trace	3.7	31.8	63.6
12d-*iso*-C_3H_7	1	---	trace	(a)	(a)	(a)
12d-*iso*-C_3H_7	2	---	trace	(a)	(a)	(a)

(a) Homogeneous sample could not be obtained for analysis since isolated fractions were oils.

Table I for pertinent physical, spectral and chromatographic properties.

Attempted Preparation of 3-Bromo- and 3,7-Dibromo-10-benzylphenothiazine.

These compounds could not be prepared by direct bromination of 10-benzylphenothiazine (**1e**). Since **1e** debenzylated under these conditions, no attempt was made to prepare these bromo compounds by other methods.

Attempted Preparation of 1,3,7-Tribromo-10-methylphenothiazine.

Methyl iodide (0.01 mole) and 0.002 mole of the sodium salt of 1,3,7-tribromophenothiazine (prepared by the action of sodamide and 1,3,7-tribromophenothiazine in liquid ammonia) were reacted for 16 hours according to the procedure of Gilman (13) to yield a mixture of 1,3,7-tribromo-10-methylphenothiazine and the unreacted tribromophenothiazine. Attempts to separate this mixture by recrystallization, column chromatography and sublimation failed. However, the R_f value and the N-CH_3 nmr band were obtained for the methylated product and are listed in Table I.

General Procedure for the Bromination of 10-Methyl, 10-Ethyl, 10-*n*-Propyl, and 10-Isopropylphenothiazines, **1a-d**, Respectively.

A solution containing 0.002 mole of bromine in 50 ml. of acetic acid was added in two liquid portions to a stirred solution of the appropriate 10-alkylphenothiazine, **1a-d**. After the addition of

each portion, the solution was stirred further until the dark red color was discharged. A drop of the clear solution was transferred to a cuvette, diluted with concentrated sulfuric acid and the visible absorption spectra of the resulting radical cations of the 3-bromo- and/or 3,7-dibromo derivatives were determined: λ max (nm): 1 equivalent of bromine, 540, 572 (**1a**), 538 (**1b** and **1c**). 541 (**1d**); 2 equivalents of bromine, 572 (**1a**), 566 (**1b** and **1c**), 571 (**1d**). (A yellow precipitate formed during the addition of the second equivalent of bromine to 10-isopropyl, **1d**, which was collected by suction and dried during which time it turned to a deep purple solid. The visible absorption spectrum of the solid was identical to that of the radical cation of 3,7-dibromo-10-isopropylphenothiazine). The solution to which two equivalents of bromine had been added was divided into two equal portions; to one portion was added a third equivalent of bromine (5×10^{-4} mole in 25 ml. of acetic acid) dropwise while a fourth equivalent of bromine (1×10^{-3} mole in 25 ml. of acetic acid) was added to the other portion. During the addition of bromine, a purple solid appeared in both reaction flasks which did not react further after 24 hours of stirring at room temperature. The purple precipitates from both reactions were collected by filtration, dried, and their visible absorption spectra were determined in nitromethane and found to be identical with that of the radical-cation (**12a-d**$^{\cdot+}$) of the corresponding 3,7-dibromo-10-alkylphenothiazine (**12a-d**).

A few crystals of the purple radical-cation solids were dissolved in acetone to give a very deep purple solution from which the color discharged upon standing. Evaporation of the acetone yielded a mixture containing bromoacetone and **12a-d**, as judged from nmr and ir spectroscopy.

The remaining radical-cation crystals from each reaction were placed in separate flasks containing 200 ml. of acetic acid and the mixtures were slowly heated to reflux during which time the radical-cation dissolved to yield a purple colored solution which subsequently changed to red, then colorless, and a green precipitate formed. After refluxing for 4 hours, the precipitate was collected by filtration (Fraction I), and the hot mother liquor allowed to cool to room temperature and refrigerated overnight. The resulting green precipitate (Fraction II) was collected by filtration and the mother liquor poured into an ice slurry to produce another batch of crystals (Fraction III) which was collected by filtration. The products in each fraction were identified by tlc analysis and the percentage yields of substances estimated from the infrared spectra of each mixture. With the exception of 10-methylphenothiazine, Fraction I was found to be essentially 1,3,7,9-tetrabromophenothiazine; Fraction III was principally 3,7-dibromo-10-alkylphenothiazine and Fraction II was composed of 1,3,7-tribromo and 1,3,7,9-tetrabromophenothiazines. In the 10-methylphenothiazine case, Fraction III also contained 1,3,7-tribromo-10-methylphenothiazine. Table I lists pertinent R_f values and nmr spectra data.

Bromination of 10-Benzylphenothiazine (**1e**).

To a stirred solution of 1×10^{-3} mole (0.291 g.) **1e** in 100 ml. of glacial acetic acid was added 5×10^{-4} mole (0.08 g.) of 15 minutes. After an additional hour of stirring the initial dark red solution gradually changed to light yellow and became lachrymatory. Tlc and ir indicated the presence of a 9:1 mixture of **1e** and phenothiazine. Further addition of 5×10^{-4} mole of bromine in 25 ml. of acetic acid over 15 minutes produced a dark red solution which after an additional 3 hours of stirring changed to deep gold. Tlc and ir indicated the presence of a 6:4 mixture of **1e** and phenothiazine. The addition of another equivalent of bromine (1×10^{-3} mole in 25 ml. of acetic acid) yielded a deep red solution which upon stirring at room temperature for 11 hours changed to a brown color and a brown precipitate formed. The mixture was filtered and tlc and ir revealed the solid material to be essentially 3,7-dibromophenothiazine and a trace of 3-bromophenothiazine and the mother liquor to be predominantly phenothiazine. The mother liquor was diluted *ca.* three-fold with water and then extracted with ether. The ether extract was washed with sodium bicarbonate, dried (magnesium sulfate) and concentrated to yield a lachrymatory substance which was distilled to yield benzyl bromide, b.p. 198-200° [lit. m.p. 198-199 (14)], nmr, s, 2H, 5.55 τ and s, 5H, 2.72 τ.

Results and Discussion

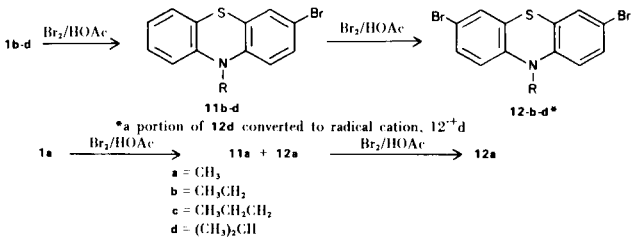
I. Bromination Studies of 10-Methyl (**1a**), 10-Ethyl (**1b**), and 10-*n*-Propyl (**1c**) and Isopropyl (**1d**) Phenothiazines.

The 10-ethyl (**1b**) and 10-*n*-propyl (**1c**) phenothiazine derivatives reacted with 1 and 2 molar equivalents of bromine in acetic acid at room temperature to produce the corresponding 3-bromo (**11b,c**) and 3,7-dibromo (**12b,c**) compounds in essentially quantitative yields (as determined by visible absorption spectroscopy of the corresponding radical-cations). For comparison, the reaction of 10-methylphenothiazine (**1a**) with a molar equivalent of bromine was repeated and found to yield an approximately 1:1 mixture of 3-bromo (**11a**) and 3,7-dibromo (**12a**) 10-methylphenothiazine.

The 10-isopropylphenothiazine (**1d**) derivative reacted with 1 molar equivalent of bromine in acetic acid at room temperature to produce the 3-bormo (**11d**) compound in essentially quantitative yield (as determined by visible absorption spectroscopy of the radical-cation).

However, reaction of **11d** with a second molar equivalent of bromine in acetic acid yielded a yellow solid whose visible absorption spectra was identical to the radical-cation (**12d**$^{\cdot+}$) of the 3,7-dibromo-10-isopropylphenothiazine (**12d**). Visible absorption spectroscopy indicated that the reaction solution contained a mixture of 3-bromo (**11d**) and 3,7-dibromo (**12d**) 10-isopropylphenothiazines. The aforementioned results are outlined in Scheme 1.

Scheme I

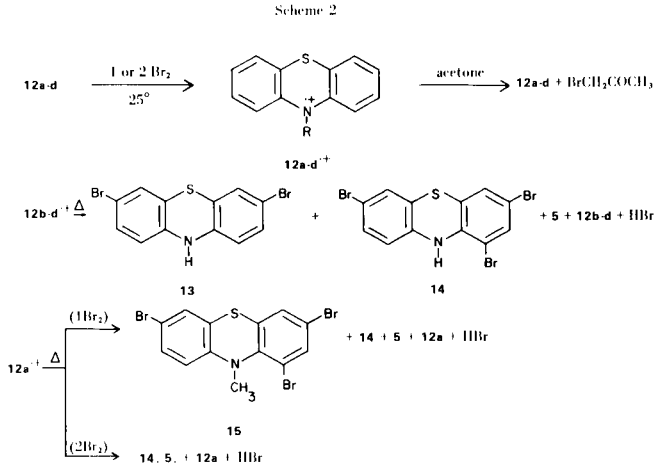


The reaction of **12a-d** with an additional 1 or 2 molar equivalents of bromine in acetic acid yielded dark purple solids whose visible absorption spectra were identical to those of radical cations (**12a-d**$^{\cdot+}$) of the corresponding 3,7-dibromo-10-alkylphenothiazine (**12a-d**) previously reported (8). Treatment of these colored solids with

acetone yielded **12a-d** and bromoacetone. In no case were higher brominated products observed in the purple precipitates. Treatment of these radical cations with refluxing acetic acid yielded predominantly 1,3,7,9-tetrabromophenothiazine (**5**) and the corresponding 3,7-dibromo-10-alkylphenothiazine (**12a-d**), smaller amounts of 1,3,7-tribromophenothiazine (**14**), and (with the exception of the 10-methyl radical cation $12^{\cdot+}$) trace amounts of 3,7-dibromophenothiazine (**13**). Hydrogen bromide gas was evolved regardless of the quantity of bromine used in generating these radical cations. The 10-methyl radical cation ($12a^{\cdot+}$) derivative (prepared from either 1 or 2 molar equivalent of bromine) did not yield any 3,7-dibromophenothiazine (**13**) but, additionally, did produce 1,3,7-tribromo-10-methylphenothiazine (**15**) upon treatment with refluxing acetic acid. Similar results were obtained from reactions in which the radical cations were isolated and subsequently treated with refluxing fresh acetic acid. Scheme 2 illustrates these reactions and Table II lists the percentage yields of the products.

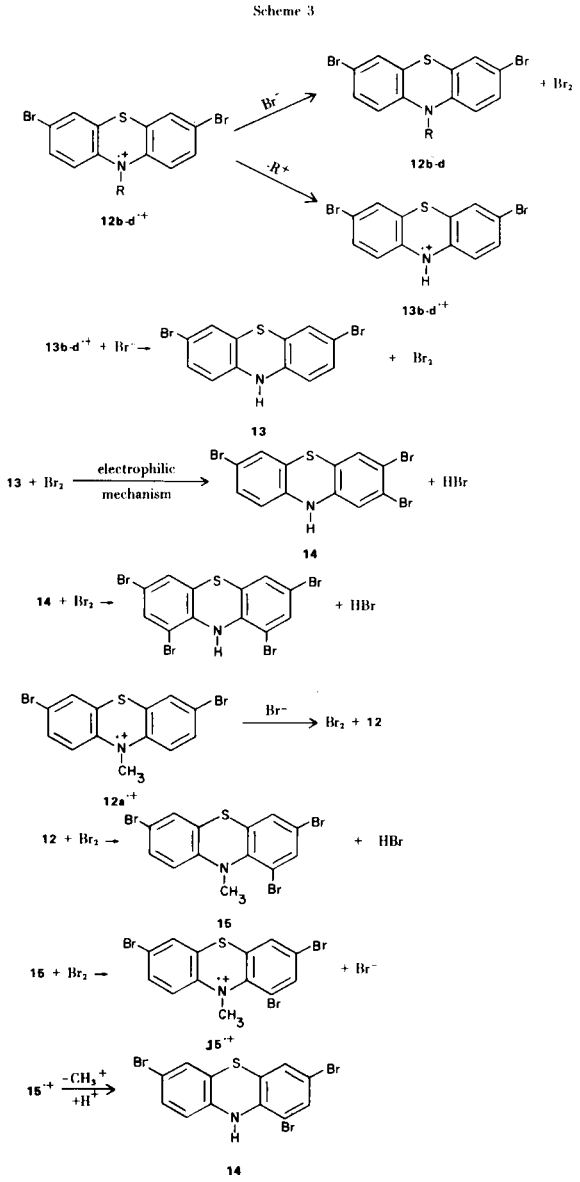
The results indicate that bromine substitution at the 3- and 7-position of phenothiazines **1a-d** proceeds via the electrophilic aromatic mechanism (Mechanism 1) since radical cations are not formed and hydrogen bromide gas is liberated. The formation of radical cation $12^{\cdot+}$**d** during addition of the second molar equivalent of bromine to 10-isopropylphenothiazine (**1d**) indicates that oxidation of 3,7-dibromo-10-isopropyl derivative (**12d**) competes successfully with electrophilic substitution at the 7-position of 3-bromo-10-isopropylphenothiazine (**11d**). Resonance stabilization of the transition state for the electrophilic substitution mechanism by lone pair electrons on nitrogen requires that these electrons be coplanar with the ring undergoing substitution. Construction of a Drieding Model reveals that the 10-isopropyl group sterically interacts with either the 1- or 9-hydrogen atom in such a conformation thereby decreasing the rate of bromination of the phenothiazine ring.

Scheme 2



The addition of the third and fourth molar equivalent to position 1 and 9 of **12a-e** might appear to proceed via the disproportionation-nucleophilic Mechanism 2 since radical cations have been isolated from these reactions. However, the evolution of hydrogen bromide and the predominant formation of 1,3,7,9-tetrabromophenothiazine upon heating these radical cations is indicative of halogenation by molecular bromine. A proposed mechanism consistent with the experimental findings is presented in Scheme 3.

Scheme 3



Thus radical cation $12a\text{-}d^{\cdot+}$ upon dissolving in hot acetic acid either reversibly undergoes electron transfer reaction with bromide ion to form molecule bromine and parent phenothiazine (**12a-d**) or irreversibly dealkylates to radical cation of 3,7-dibromophenothiazine ($13^{\cdot+}$). Radical

cation **13**$^{\cdot+}$ may then undergo a similar electron transfer reaction with bromide ion to produce parent phenothiazine (**13**) and bromine. Bromine formed in these redox reactions then may brominate the phenothiazine nucleus via the typical electrophilic aromatic substitution mechanism. Bromination of 3,7-dibromo-10-alkylphenothiazine (**12a-d**) occurs only with 10-methyl compound (**12a**) indicating that the groups larger than methyl hinder the addition of bromine to the 1 position. Dealkylation of **12b-d** must occur initially to allow subsequent bromination at positions 1 and 9.

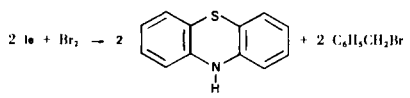
The formation of bromoacetone from the reaction of radical cations and bromide ion in acetone solution clearly demonstrates that molecular bromine is produced from these ions.

$$2\dot{N}^{+} + 2Br^{-} \xrightarrow{\text{acetone}} Br_2 + 2\ddot{N}$$ (only nitrogen atom of radical cation shown)

$$Br_2 + CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \rightarrow Br\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 + HBr$$

II. Bromination Study of 10-Benzylphenothiazine (**1e**).

Treatment of 10-benzylphenothiazine (**1e**) with one molar equivalent of bromine at room temperature failed to yield any appreciable amount of the corresponding 3-bromo- or 3,7-dibromo-10-benzyl derivative. Instead, **1e** dealkylated in part under these conditions to phenothiazine (**17**) and benzyl bromide. Further bromination of this reaction mixture and stirring for 11 hours (1 molar



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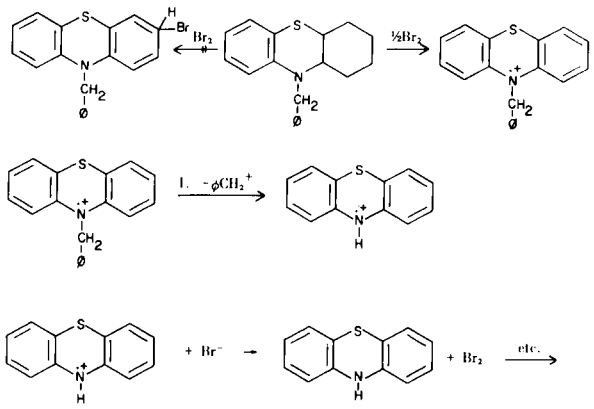
equivalent) resulted in the complete dealkylation of **1e** and the formation of 3,7-dibromophenothiazine (**13**) and a trace of 3-bromophenothiazine. Again, no brominated 10-benzyl compounds were observed.

The retardation of nuclear bromination by 10-alkyl substituents first observed in the reaction of 10-isopropylphenothiazine (**1d**) is more dramatically revealed in the bromination of 10-benzylphenothiazine (**1e**). The large size of the benzyl group apparently reduces the resonance participation of the lone pair nitrogen electrons to such an extent that nuclear bromination cannot compete with formation of radical **1e**$^{\cdot+}$. The results also show that debenzylation of **1e** must occur prior to nuclear bromination. The data do not allow a choice as to whether dealkylation occurs via radical cation or dication of **1e**. However, the greater ease of dealkylation of the benzyl group as compared to the other groups in this study (e.g. methyl, etc.) is consistent with an S_N1 process. The radical cation of phenothiazine thus produced then undergoes electron transfer with bromide ion to phenothiazine which

Scheme 4



is subsequently brominated via a typical aromatic substitution mechanism. These steps are summarized in Scheme 4.

We currently are studying the dealkylation of substituted benzylphenothiazine in order to glean additional information on the dealkylation step.

REFERENCES AND NOTES

(1a) Supported in part by grants from The Robert A. Welch Foundation; (b) Robert A. Welch Predoctoral Fellow.

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