Improved Synthesis of 3-Bromo-10-methyl- and 3-Bromo-10-ethylphenothiazines (1a)

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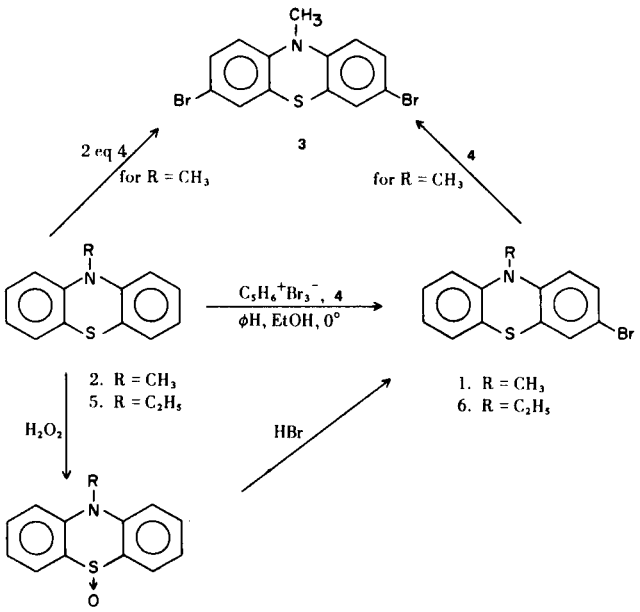
During the course of our investigation of the synthetic and theoretical aspects of the aryne reaction, it became necessary to acquire substantial quantities of 3-bromo-10-methylphenothiazine (**1**). The only previously reported (2) synthesis of **1** involves the reaction of 10-methylphenothiazine (**2**) with bromine in glacial acetic acid at room temperature. However, the yield of **1** by this method is very poor (< 10%), presumably due to the high reactivity of bromine towards **2**. The investigation of a less reactive brominating agent was thus pursued.

Pyridinium hydrobromide perbromide (**4**) a mild, selective brominating agent, has been extensively used in the bromination of ketones (3a, b), olefins (4a, b), and ketals (5a, b). Bromination of aromatic and heterocyclic compounds with **4** has not been as widely used even though **4** selectively brominates certain compounds of this type under mild conditions. For example, **4** is reported to be the most satisfactory reagent for the conversion of indole into 3-bromoindole (6). Also, utilization of **4** as an analytical reagent for phenols (4b) has been described. However, the limited use of **4** in heterocyclic brominations is illustrated by its total absence in Eisch's elegant review (7) on this subject.

We wish to report an improved synthesis of **1** (90% crude; 45% pure) by the low temperature (0°) bromination of **2** using pyridinium hydrobromide perbromide, **4**, in ethanol/benzene solvent. Attempts to prepare a pure authentic sample of **1** by the method of Bodea and Terdic (2) were unsuccessful. Indeed, the purity of **1**, having a melting point range of 112-116° so reported by these workers, is suspect. Therefore, characterization of **1** was carried out. Elemental analysis, and the nmr and mass spectra were consistent with the proposed structure of **1**. That the nmr spectrum of **1** was duplicated by the superimposition of the nmr spectra of 10-methylphenothiazine (**2**) and the corresponding 3,7-dibromo derivative, **3**, confirmed the position of the 3-bromo atom in **1**.

Compound **1** was also synthesized (51%) by the reductive bromination of 10-methylphenothiazine 5-oxide in the presence of 48% hydrobromic acid by the method of Gilman and coworkers (8). This reaction had been reported to yield only inextractable tar (9). However, the reaction mixture was found to crystallize upon standing overnight. A thin-layer chromatogram indicated that **3** was also present in the crude crystallized product, further supporting the electrophilic mechanism (8) for the reductive halogenation of 5-oxo compounds.

REACTION SCHEME



Finally, treatment of either the mono bromo derivative **1** or **2** with 1 eq or 2 eq, respectively, of the perbromide **4** yielded 3,7-dibromo-10-methylphenothiazine (**3**) (85-92%), as judged by mixed melting point, nmr, mass spectroscopy and elemental analysis. The nmr spectrum of **3** exhibited a typical AB aromatic quartet pattern consistent with either 3-7, 3-8, 2-7, or 2-8 dibromo-substitution. However, bromination of the 2- or 8-position of the phenothiazine nucleus is unlikely since the nitrogen atom in this system exerts a strong "*ortho-para*" directing effect. For example, 1,3,7,9-tetrachlorophenothiazine or 1,3,7,9-tetrabromophenothiazine are the major products when phenothiazine is treated with four

equivalents of chlorine (10) or bromine (11), respectively.

Interestingly, *N*-bromosuccinimide (NBS), which brominates various 2- and 3-substituted thiophenes under remarkably mild conditions (12) was not capable of monobrominating **2**; all attempts produced the 3,7-dibromo derivative, **3**.

Perbromide (**4**) was also found to convert 10-ethylphenothiazine (**5**) into 3-bromo-10-ethylphenothiazine (**6**) in good yield (78% crude; 47% isolated yield). Identity of **6** was confirmed by mixing melting point and spectral comparison with authentic sample of **6** produced by the method of Gilman. The yield of **6** as obtained in this study is superior to that previously reported (20%) (8).

In conclusion, the monobromination of 10-methyl- and 10-ethylphenothiazine (**2** and **5**, respectively) to the corresponding 3-bromo derivatives (**1** and **6**, respectively) can be accomplished by the use of pyridinium hydrobromide perbromide (**4**). The high selectivity of **4** towards the phenothiazine nucleus is probably due to the very low concentration of elemental bromine in equilibrium with the perbromide **4**.

EXPERIMENTAL

Preparation of Starting Materials or Authentic Samples Previously Reported.

N-Methylphenothiazine was prepared by the method of Gilman *et al.* for the *N*-ethyl compound (13). Crystallization from benzene gave m.p. 98°; lit. (14) m.p. 99°. *N*-Ethylphenothiazine was prepared in a similar manner. Crystallization from 2-propanol gave m.p. 100-101°; lit. (13) 103-104°. Pyridinium hydrobromide perbromide was prepared by the method of Fieser (3a). *N*-Methylphenothiazine *S*-oxide was prepared as described by Schmalz and Burger (9). Crystallization from 2-propanol gave m.p. 194-196°; lit. (9) 193°. *N*-Ethylphenothiazine 3-oxide was prepared as described by Gilman and Eisch (8). Recrystallization from 2-propanol gave m.p. 161-163°; lit. (8) 162-163°. 3-Bromo-10-ethylphenothiazine was prepared as described by Gilman and Eisch (8). Recrystallization from 2-propanol, then petroleum ether, gave m.p. 123-124°; lit. (8) 123-124°.

Preparation of 3-Bromo-10-methylphenothiazine (**1**).

a. From 10-Methylphenothiazine and Pyridinium Hydrobromide Perbromide (**4**).

In a typical experiment, 4 g. (0.019 mole) of **2** was dissolved in 35 ml. of benzene. After 35 ml. of ethanol was added, the solution was cooled to 0° with stirring. Then **4** (6 g., 0.019 mole) recrystallized from glacial acetic acid prior to use, was added in portions over a period of 45 minutes. After the addition of **4** was complete, the yellow solution was stirred for an additional 10 minutes and then placed in a separatory funnel containing 100 ml. of water. The top benzene layer was removed and the bottom aqueous-alcohol layer was extracted with three 50-ml. portions of benzene. The benzene extracts were combined, dried (magnesium sulfate) and then evaporated to yield 4.9 g. (09%) of **1**, m.p. 97-100°. Thin layer chromatography, using silica gel with fluorescent indicator sheets (Eastman Chromatogram Sheet 6060) and petroleum ether (30-60°) as developing solvent indicated that the crude reaction product was slightly contaminated with 3,7-dibromo-10-methylphenothiazine (**3**) and starting material (**2**). The identity of **1**, **2**, and **3** was established by spotting known samples of each substance alongside the crude product and comparing their R_f values (0.79, 0.84, 0.62; 1, 2, 3, respectively) in the developed chromatogram. Repeated recrystallization from 2-propyl alcohol yielded 2.4 g. (45%) of an analytical sample, m.p. 112-112.5°. The mass spectrum contained a parent peak, P, at 291 (theoretical 291) and an equally intense P + 2 peak, indicative of a monobromo derivative. Characteristic P - 15 and P - 13 peaks (N - CH_3 fragmentation) and P - 80 and P - 78 peaks (C - Br fragmentation) were also observed. The nmr spectrum (CS_2) consisted of: 3 H(s) τ 6.92 (N - CH_3) and 7 H(m) τ 2.79-3.58 (aromatic H).

Anal. Calcd. for $C_{13}H_{10}BrNS$: C, 53.44; H, 3.45; Br, 27.35; N, 4.79; S, 10.97. Found: C, 53.82; H, 3.57; Br, 27.37; N, 4.73; S, 10.50.

b. From **2** *via* the *S*-Oxide.

A mixture of 3.41 g. (0.014 mole) of 10-methylphenothiazine *S*-oxide, 6.6 ml. of 48% hydrobromic acid and 6.6 ml. of water was stirred for 30 minutes at room temperature and then refluxed for one hour. The mixture was then cooled to room temperature, at which time a green tar separated. The reaction liquid was decanted and, upon standing overnight, 2.2 g. (51%) of the green tar crystallized. Recrystallization from 2-propanol gave m.p. 112-112.5°, which was not depressed upon admixture of **2** prepared as described in (a) above.

Preparation of 3,7-Dibromo-10-methylphenothiazine (**3**).

a. Treatment of Mono-bromo Derivatives (**1**) with Perbromide (**4**).

To a stirred solution containing 2.9 g. (0.01 mole) of **1**, 30 ml. of benzene and 30 ml. of ethanol was added 3.2 g. (0.01 mole) of **4** in portions over a 30-minute period. After stirring for an additional 30 minutes, the solution was worked up in a similar manner as described previously in the monobromination of **2** to give 3.2 g. (86%) of **3**, which after three recrystallizations from 2-propanol gave 1.6 g. (43%), m.p. 151-152°. Mass spectral pattern: parent peak, P, 369 (theoretical 369): P, P + 2, and P + 4 peaks in the ratio of 1:2:1, respectively (indicative of a dibromo compound): P - 15, P - 13, P - 11 (fragmentation of N - CH_3) and P - 80, P - 78, P - 76 (loss of bromine); nmr spectrum (carbon disulfide) showed a singlet (3 H) τ 6.70 band as well as a typical AB aromatic quartet pattern, H_A, 3.53 τ; H_B, 2.89 τ (J_{AB} = 8 Hz) (4 H) and a singlet at 2.97 τ (2 H).

Anal. Calcd. for $C_{13}H_9Br_2NS$: C, 42.08; H, 2.44; Br, 43.07; N, 3.77; S, 8.64. Found: C, 41.85; H, 2.72; Br, 43.27; N, 3.32; S, 8.12.

b. Treatment of 10-Methylphenothiazine (**2**) with 2 Equivalents of **4**.

In a similar manner to that described in (a) above, 2.9 g. (0.0135 mole) of **2**, 8.7 g. (0.027 mole) of **4** in 30 ml. of benzene and 30 ml. of ethanol were converted to 4.6 g. (92%) of **3**. Recrystallization from 2-propanol gave 3.3 g. (66%) of **3**, m.p. 143-145°, which was raised to 151-152° after two additional recrystallizations from 2-propanol. No depression in the m.p. was observed by admixing a sample of **3** prepared as described in (a) above.

Preparation of 3-Bromo-10-ethylphenothiazine (**5**).

A 3-g. sample (0.0132 mole) of **5** and 4.3 g. (0.0132 mole) of **4** were treated in a manner similar to that described previously in the preparation of the corresponding 10-methyl derivative to

yield 2.9 g. (70%) of **6** after one recrystallization from petroleum ether (30-60°), m.p. 112-116°. Further recrystallization from petroleum ether yielded 1.9 g. (47%) pure crystals of **6**, m.p. 123-124°) which was not depressed by admixing a sample of **6** produced by the method of Gilman (8).

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