Anal. Calcd for $C_{12}H_{13}N_3O$: C, 59.26; H, 5.35; N, 28.81. Found: C, 59.15; H, 5.43; N, 28.71.

6-[(Methoxymethyl)ethynyl]pterin (5d): 82 mg (88%) of a yellow microcrystalline powder; mp >300 °C; NMR (Me_2SO-d_6) δ 3.34 (s, 3 H), 4.38 (s, 2 H), 7.0 (br, 2 H), 8.71 (s, 1 H), 11.6 (br, 1 H); IR (KBr) 3000–3500 (br), 2240 (w), 1700 (br) cm^{-1}.

Anal. Calcd for $C_{10}H_9N_5O_2 \cdot 0.35\ H_2O$: C, 50.57; H, 4.12; N, 29.49. Found: C, 50.56; H, 3.97; N, 29.47.

2-Pivaloyl-6-chloropterin (7). A suspension of 6-chloropterin (6) (10.86 g, 0.055 mol) and 4-(dimethylamino)pyridine (1 g, 8.1 mmol) in pivalic anhydride (50 mL) was heated under reflux for 6 h. The mixture was cooled to room temperature, diluted with ether (300 mL), and then held at 2 °C for 2 h. The precipitated solid was collected by filtration, dissolved in dichloromethane, and passed through a pad of silica gel, by eluting with 2% methanol in dichloromethane. Evaporation of the filtrate under reduced pressure and recrystallization of the residual solid from ethanol gave 11.1 g (72%) of cream-colored microcrystals: mp 272–273 °C; NMR ($CDCl_3$) δ 1.36 (s, 9 H), 8.50 (br, 1 H), 8.80 (s, 1 H), 12.3 (br, 1 H) [the presence of a very small amount of ethanol in the sample was readily apparent from the NMR spectrum and confirmed by microanalysis]; IR (KBr) 3020–3350 (br), 1730, 1610 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}ClN_5O_2 \cdot 0.35C_2H_5OH$: C, 47.18; H, 4.77; N, 23.51; Cl, 11.90. Found: C, 47.44; H, 4.70; N, 23.70; Cl, 11.77.

General Procedure for Palladium-Catalyzed Coupling of 2-Pivaloyl-6-chloropterin with Acetylenes. A mixture of 2-pivaloyl-6-chloropterin (1 g, 3.552 mmol), palladium acetate (100 mg, 0.445 mmol), tri-*o*-tolylphosphine (277 mg, 0.91 mmol), copper(I) iodide (85 mg, 0.445 mmol), triethylamine (5 mL), the appropriate acetylene (4 mmol), and acetonitrile (20 mL) was heated under nitrogen at reflux for 8 h. The solvent was removed by evaporation under reduced pressure, and the residue was chromatographed on silica gel, by eluting with 1% methanol in chloroform. The fractions containing the product were combined, the solvent was removed in vacuo, and the residual solid was recrystallized.

2-Pivaloyl-6-(phenylethynyl)pterin (8a). Recrystallization from absolute ethanol gave 678 mg (55%) of cream-colored microcrystals: mp 284–285 °C; NMR ($CDCl_3$) δ 1.37 (s, 9 H), 7.38–7.45 (m, 3 H), 7.62–7.65 (m, 2 H), 8.41 (br, 1 H), 8.96 (s, 1 H), 12.30 (br, 1 H); IR (KBr) 3020–3360 (br), 2220, 1680, 1620 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.71; H, 4.90; N, 20.17. Found: C, 65.70; H, 4.95; N, 20.14.

2-Pivaloyl-6-(*n*-butylethynyl)pterin (8b). Recrystallization from absolute ethanol gave 824 mg (71%) of yellow microcrystals: mp 242–243 °C; NMR ($CDCl_3$) δ 0.96 (t, 3 H, J = 7.16 Hz), 1.35 (s, 9 H), 1.42–1.64 (m, 4 H), 2.50 (t, 2 H, J = 7.18 Hz), 8.39 (br, 1 H), 8.80 (s, 1 H), 12.37 (br, 1 H); IR (KBr) 3020–3320 (br), 2240, 1690, 1620 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.38; H, 6.42; N, 21.40. Found: C, 62.26; H, 6.49; N, 21.36.

2-Pivaloyl-6-(*tert*-butylethynyl)pterin (8c). Recrystallization from absolute ethanol gave 813 mg (70%) of a cream-colored microcrystalline solid: mp 327–328 °C; NMR ($CDCl_3$) δ 1.35 (s, 9 H), 1.36 (s, 9 H), 8.38 (br, 1 H), 8.81 (br, 1 H), 12.20 (br, 1 H); IR (KBr) 3020–3340 (br), 2230, 1690, 1615 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.38; H, 6.42; N, 21.40. Found: C, 62.23; H, 6.51; N, 21.31.

2-Pivaloyl-6-[(methoxymethyl)ethynyl]pterin (8d). Recrystallization from absolute ethanol gave 627 mg (56%) of cream-colored microcrystals: mp 225–226 °C; NMR ($CDCl_3$) δ 1.36 (s, 9 H), 3.49 (s, 3 H), 4.39 (s, 2 H), 8.45 (br, 1 H), 8.86 (s, 1 H), 12.45 (br, 1 H); IR (KBr) 3040–3300 (br), 1680, 1620 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}N_5O_3$: C, 57.14; H, 5.39; N, 22.22. Found: C, 56.89; H, 5.47; N, 22.11.

General Procedure for Preparation of the Pterins 5a–d by Hydrolysis of the Corresponding 2-Pivaloylpterins 8a–d. The 2-pivaloylpterin (0.4 mmol) was heated 6–8 h under reflux with 1.5 N NaOH in 95% ethanol. The progress of the hydrolysis was monitored by TLC. The solvent was removed by evaporation under reduced pressure, and the residual solid was dissolved in water (10 mL). Acidification with acetic acid, cooling to 2 °C for 18 h, and filtering gave a solid, which was washed sequentially with water, ethanol, and ether and dried at 80 °C in vacuo.

Compounds **5a–d** obtained by the above procedure were identical in every respect with the compounds prepared as described above by hydrolysis of the appropriate 2,4-diaminopteridines **4a–d**. Observed yields were as follows: **5a**, 97 mg (92%); **5b**, 84 mg (86%); **5c**, 82 mg (85%); **5d**, 81 mg (88%).

Registry No. **1**, 25911-65-3; **2**, 17231-51-5; **3a**, 108472-96-4; **3b**, 108472-97-5; **3c**, 108472-98-6; **3d**, 108472-99-7; **4a**, 108473-00-3; **4b**, 108473-01-4; **4c**, 108473-02-5; **4d**, 108473-03-6; **5a**, 108473-04-7; **5b**, 108473-05-8; **5c**, 108473-06-9; **5d**, 108473-07-0; **6**, 64507-68-2; **7**, 108473-08-1; **8a**, 108473-09-2; **8b**, 108473-10-5; **8c**, 108473-11-6; **8d**, 108473-12-7; PhC≡CH, 536-74-3; $CH_3(CH_2)_3C{\equiv}CH$, 693-02-7; $(CH_3)_3CC{\equiv}CH$, 917-92-0; $CH_3OCH_2C{\equiv}CH$, 627-41-8; guanidine hydrochloride, 50-01-1.

First Synthesis of Sulfoxides and Sulfones in the 3*H*-Phenothiazin-3-one and 5*H*-Benzo[*a*]phenothiazin-5-one Ring Systems. Addition Reactions with Nucleophiles

Yves Girard,* Pierre Hamel,* Michel Thérien, James P. Springer,† and Jordan Hirshfield†

Merck Frosst Canada Inc., Pointe Claire-Dorval, Quebec, Canada H9R 4P8, and Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Received January 22, 1987

We report the first synthesis of sulfoxides and sulfones in the 3*H*-phenothiazin-3-one and 5*H*-benzo[*a*]-phenothiazin-5-one ring systems. The pronounced reactivity of the parent compounds **2a**, **2b**, **4a**, and **4b** does not allow their isolation, but they can be conveniently trapped, as various types of adducts, with nucleophiles such as water, alcohols, and amines. The monoadduct **16b** of 3-oxo-3*H*-phenothiazine 5,5-dioxide with *n*-propylamine rearranges into a derivative of the novel oxazolo[5,4-*c*]phenothiazine ring system (**17**).

Introduction

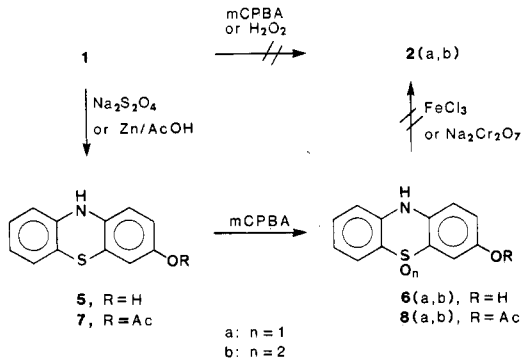
The scope of interest in phenothiazine derivatives covers a wide assortment of areas. Complexes such as Methylene Blue are well-known as dyes, bacteriological stains, or redox indicators, while other types of derivatives have been reported as antioxidants,[1] antiseptics,[2] insecticides,[3] anthelmintics,[4] etc.

† Rahway, NJ.

(1) Stiner, H. M. *Proc. Annu. Meet. N. Y. State Hortic. Soc.* **1945**, *199*, 195.
(2) Thomas, J. O. *J. Pharmacol. Exp. Ther.* **1938**, *64*, 280.
(3) Hervikva, J.; Kello, V. *Chem. Zvesti* **1973**, *127*, 249.
(4) Gordon, H. McL.; Lipson, M. J. *Counc. Sci. Ind. Res.* (*S.A.*) **1940**, *13*, 173.

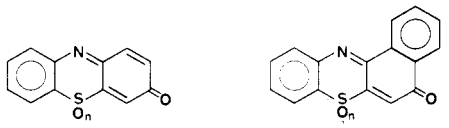
0022-3263/87/1952-4000$01.50/0

Scheme I



N-Alkylation of Phenothiazine has led to pharmaceutically important substances, such as Promethazine (antihistaminic),[5] Ethopropazine (anti-Parkinson),[6] and Dimethoxanate (antitussive).[7] The discovery of the antipsychotic agent Chlorpromazine[8] in the early 1950s and the appearance since of even more potent phenothiazine psychopharmacological agents constitute a landmark event in the history of the medical and psychiatric sciences.

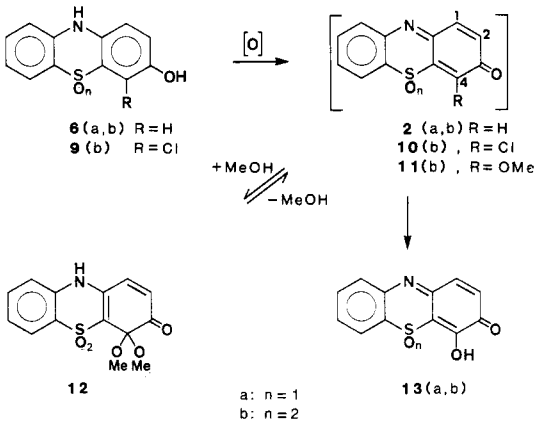
Derivatives bearing the 3*H*-phenothiazin-3-one (**1**) backbone are known to derive from chemical[9,12] or metabolic[10] oxidation of phenothiazines and many direct syntheses have also been reported.



Numerous examples of phenothiazines in which the sulfur atom is present in higher oxidation states (sulfoxide, sulfone) can be found in the chemical literature;[11] however, this is not true in the case of derivatives in which the nucleus itself exists in a higher oxidation state, characterized by a quinonoid-type arrangement such as found in 3*H*-phenothiazin-3-one (**1**). Indeed we are unaware of any previous report of the preparation of sulfoxides or sulfones in derivatives of this type; although 3-oxo-3*H*-phenothiazine 5-oxide (**2a**) is suspected of being an intermediate in the air-oxidation process which slowly transforms 3*H*-phenothiazin-3-one into 7-hydroxy-3*H*-phenothiazin-3-one (Thionol),[12] it has never been isolated or characterized. The same holds true for the *S*-oxides of the related 5*H*-benzo[*a*]phenothiazin-5-one (**3**) family of compounds.

The observation in our laboratories of interesting leukotriene inhibitory properties of several 3*H*-phenothiazin-3-one derivatives[13] prompted us to investigate the synthesis of derivatives bearing sulfur in higher oxidation states.

Scheme II



In the present paper, we describe the first in situ preparation of the sulfoxides and sulfones of 3*H*-phenothiazin-3-one (**2a,b**) and of 5*H*-benzo[*a*]phenothiazin-5-one (**4a,b**) and their pronounced susceptibility toward nucleophilic additions.

Results and Discussion

I. Preparation of *S*-Oxides of 3*H*-Phenothiazin-3-one. Attempts to oxidize 3*H*-phenothiazin-3-one (**1**) with several oxidizing agents, (e.g., hydrogen peroxide, *m*-chloroperoxybenzoic acid, etc.) did not lead to any isolable amounts of **2a** or **2b** (Scheme I).

The well-known facile oxidation of 3-hydroxy-10*H*-phenothiazine (**5**) to 3*H*-phenothiazin-3-one (**1**), by mild oxidizing agents or by atmospheric oxygen,[12,14] suggested an alternative approach to the preparation of **2a** and **2b**. Bodea and Panea[15] described the direct oxidation of **5**, using perbenzoic acid, to the corresponding sulfoxide **6a** and sulfone **6b** (Scheme I); we considered these to be ideal precursors, via a subsequent ring-oxidation process, of the corresponding **2a** and **2b**.

Unsatisfactory results in the direct oxidation of **5** to **6a,b** led us to use an indirect route, via the acetate **7** which offered better control over the oxidation step (Scheme I).

Initial attempts to oxidize **6a** and **6b** to the desired **2a** and **2b**, using ferric chloride or sodium dichromate in methanol or aqueous methanol, led to mixtures from which no identifiable entity could be recovered.

However, oxidation of **6a** and **6b** using a large excess of sodium chlorite[16] in acidic aqueous medium (2% H_2SO_4) led to the rapid formation of highly insoluble, red-orange substances that were identified as 4-hydroxy-3-oxo-3*H*-phenothiazine 5-oxide (**13a**) and 5,5-dioxide (**13b**) (Scheme II), respectively, presumably resulting from 1,4-addition of the elements of water to **2a** and **2b**, followed by a second oxidation step. The assignment of structure was based on the spectral data of **13b**. Thus the 300-MHz ^1H NMR spectrum (Me_2SO-d_6) reveals the absence of proton at C-4, the presence of an exchangeable proton (12.39 ppm), and a pair of doublets at 6.77 and 7.30 ppm (J = 10.3 Hz), indicating the presence of the olefinic protons (H_1 and H_2). Decoupling experiments allow the unequivoqual assign-

(5) Charpentier, P. *C. R. Hebd Seances Akad. Sci.* **1947**, *225*, 306.
(6) U.S. Pat. 2607773, 1952 (Rhône-Poulenc).
(7) U.S. Pat. 2778824, 1957 (American Home Prod.).
(8) Charpentier; et al. *C. R. Hebd Seances Akad. Sci.* **1952**, *235*, 59.
(9) Bodea, C.; Raileanu, M. *Liebigs Ann. Chem.* **1958**, *641*, 171.
(10) Alexander, F.; Mackie, A.; Ghatge, N.; Waddell, A. W. *Arch. Int. Pharmacodyn. Ther.* **1958**, *113*, 254.
(11) Saraf, S.; Khan, M. A.; Al-Mousawi, S. *Heterocycles* **1983**, *20*, 283 and references therein.
(12) Craig, J. C.; Tate, M. E. *Prog. Drug Res.* **1961**, 3, 81.
(13) (a) Guindon, Y.; Fortin, R.; Lau, C. K.; Rokach, J.; Yoakim, C. European Patent Application EP 115394, Aug 1984; *Chem. Abstr.* **1984**, *101*, 230555t. (b) Guindon, Y.; Girard, Y.; Maycock, A.; Ford-Hutchinson, A. W.; Atkinson, J. G.; Dallob, A.; Desousa, D.; Dougherty, H.; Egan, R.; Ham, E.; Fortin, R.; Hamel, P.; Lau, C. K.; Leblanc, Y.; McFarlane, C. S.; Piechuta, H.; Thérien, M.; Yoakim, C.; Rokach. J. *Prostaglandins and Related Compounds*, in Advances in Prostaglandin Thromboxane and Leukotriene Research; Raven Press: New York, 1987; Vol. 17A, 554.
(14) (a) Bodea, C.; Raileanu, M. *Liebigs Ann. Chem.* **1958**, *614*, 171. (b) Bodea, C.; Broser, E. *Rev. Roum. Chim* **1969**, *14*, 1617.
(15) (a) Bodea, C.; Panea, T. Fr. Pat. 2105307, 1972; *Chem. Abstr.* **1972**, *77*, 164765u. (b) Bodea, C.; Panea, T. Fr. Pat. 2102567, 1972; *Chem. Abstr.* **1972**, *77*, 164720a.
(16) Logan, C. D.; Husband, R. M.; Purves, C. B. *Can. J. Chem.* **1955**, *33*, 82.

ment of signals to each of the four aromatic protons (H_6–H_9).

From the IR spectrum additional evidence was supplied by the broad absorption in the OH stretching region of the spectrum (3600–2900 cm^{-1}) and strong bands characteristic of carbonyl (1698 cm^{-1}) and sulfone (1315, 1145 cm^{-1}) absorptions. Further proof of structure was obtained by reduction of **13b** with sodium hydrosulfite, affording 3,4-dihydroxy-10*H*-phenothiazine 5,5-dioxide, which was duly characterized. The isolation of **13a,b** as trapped forms of **2a,b** represented the first evidence of the actual in situ generation of the latter. More direct evidence was obtained when it was possible to observe **2b** in solution by 300-MHz ^1H NMR, after addition of DDQ to a solution of **6b** in THF-d_8. The signal for the proton at H_4 of **2b** is clearly visible as a sharp doublet (J = 2 Hz) at 7.34 ppm, shifted slightly downfield from its counterpart in **6b** (7.26 ppm). A strong downfield shift for the signal assigned to H_1 (7.43 vs. 7.03 ppm) and an upfield shift for that of H_2 (6.70 vs. 6.97 ppm) are also in agreement with the structure of **2b**. A complete description of the spectra is included in the Experimental Section. Although **2b** exists in solution and can be easily observed, all attempts at isolation led to complex mixtures.

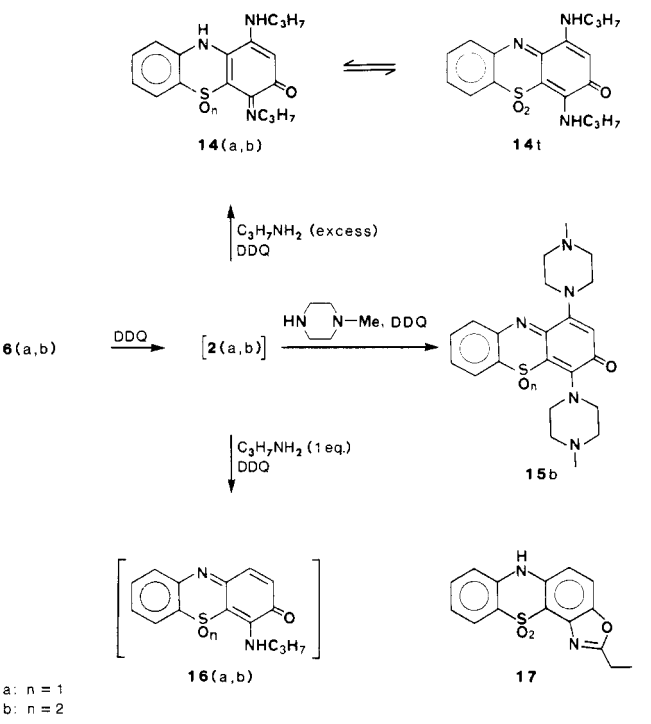
This enhanced reactivity toward nucleophilic attack at the 4-position is also demonstrated when 4-chloro-3-hydroxy-10*H*-phenothiazine 5,5-dioxide (**9b**) is submitted to the sodium chlorite oxidation described above, leading to rapid precipitation of **13b** from the reaction mixture. This product results from initial attack of water onto the in situ generated **10b**, with subsequent elimination of HCl.

Addition of Nucleophiles to 2a,b. The trapping of the phenothiazinone sulfoxides and sulfones by water to give the hydroxy adducts **13a** and **13b** denotes a strong enhancement of the electrophilic character at the 4-position of the nucleus. An obvious extension was to examine the possibility of trapping with other types of nucleophiles.

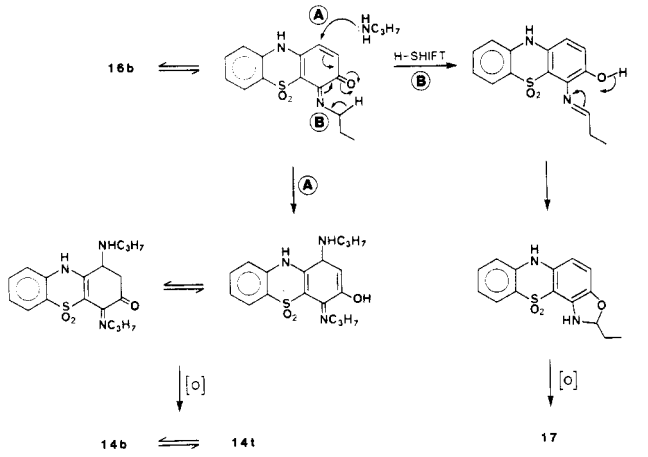
On treatment of **6b** with excess DDQ in methanol, at room temperature, there is formation of a green solution which after a few minutes deposits a yellow crystalline solid. The IR spectrum (KBr) of this substance shows sharp absorption at 3290 cm^{-1} and the ^1H NMR spectrum (Me_2SO-d_6) reveals a sharp singlet at 3.25 ppm, integrating for two methoxy groups and two sharp doublets at 6.51 and 7.24 ppm (J = 10 Hz), assigned to the protons H_1 and H_2, respectively. These data suggested that this substance is not the monoadduct **11b**, but rather the geminal 4,4-dimethoxy adduct **12** (Scheme II) resulting from a second conjugate addition of the elements of methanol to **11b**. This diadduct has limited stability, and on standing in air slowly transforms into a bright red solid which corresponds to the 4-hydroxy adduct **13b**. We believe that this last process is initiated by 1,4-elimination of the elements of methanol, regenerating the monoadduct **11b** which is easily hydrolyzed by atmospheric moisture to **13b**.

Oxidation of **6a** and **6b** with an excess of DDQ in THF also affords an initial green solution and subsequent addition of a large excess of a primary or secondary amine (e.g., *n*-propylamine or *N*-methylpiperazine, Scheme III) causes the immediate appearance of a deep red coloration, due to highly colored, stable adducts whose ^1H NMR spectra once again reveal the incorporation of two molecules of the nucleophile. However, the presence of a singlet at ca. 5.5 ppm in all cases indicates that, after initial addition at C-4 and reoxidation, a second addition has occurred at either C-1 or C-2 to afford a 1,4- or 2,4-diadduct. Since spectral data were not adequate to establish the actual structure of these adducts, X-ray diffraction studies

Scheme III



Scheme IV



were performed on the diadduct resulting from addition of excess *n*-propylamine onto preformed **2b**. The solution of the crystal structure clearly demonstrated that the substitution pattern was 1,4 rather than 2,4 (Figure 1, supplementary material). In addition, in the crystal the structure is a combination of both ortho and para quinone imine forms (**14b** and **14t**) as evidenced by the geometry. For instance, the N10–C10A bond length is 1.27 Å and the N16–C4 bond length is 1.31 Å compared to a single C-(sp^2)–N bond length of 1.38 Å for N11–C1. Also the length of the C4–C4A (1.38 Å) and C4A–C10A (1.47 Å) bonds are intermediate between pure single and pure double bonds.

In contrast, the ^1H NMR data indicate that, in solution, the ortho quinoneimine tautomer **14b** is the only one observed. Based on these data, we have assigned the structure **14b** to this diadduct and **14a** to the corresponding sulfoxide.

Similarly, 1,4-diadduct **15b** is obtained by trapping preformed **2b** with a large excess of *N*-methylpiperazine.

A plausible mechanistic pathway for the formation of these diadducts, using **14b** as an example, is illustrated in Scheme IV (path A). Initial attack of the amine at C-4, followed by oxidation, leads to intermediate monoadduct

16b. At this point subsequent attack of a second molecule of nucleophile could conceivably occur at C-2, but a very active equilibrium between **16b** and its ortho quinone imine tautomer, resulting in a pronounced "push-pull" effect, appears to favor attack at C-1. Ultimate reoxidation then leads to final product **14b**.

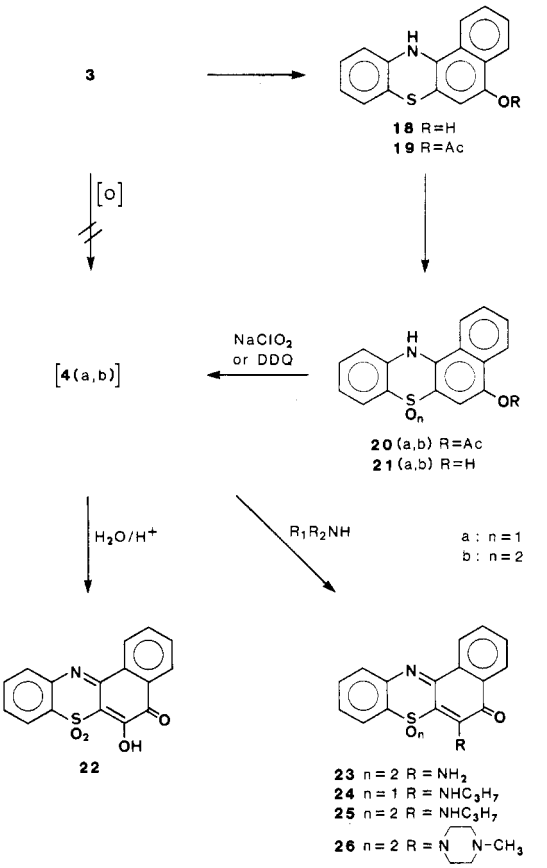
The rapid addition of amines onto **2a,b** is in direct contrast with the known reactivity of 3*H*-phenothiazin-3-one (**1**) toward amines which leads under more drastic conditions to amination at the 2-position.[17]

The possible intermediacy of C-4 monoadduct **16b** prompted attempts at its isolation. In a carefully monitored experiment, the addition of a slight excess of 1 mol of *n*-propylamine to the solution of preformed **2b** described above also led to the generation of a dark red coloration. TLC monitoring revealed a bright red substance slightly more polar than diadduct **14b**. Attempts to isolate this material, assumed to be monoadduct **16b**, by rapid flash chromatography, led to the elution of a more complex mixture than had been originally injected onto the column. From some of the fractions a light colored, sparingly soluble substance crystallized, whose ^{1}H NMR spectrum revealed the elements of an *ethyl* moiety! Mass spectral analysis (*m/e* 300) and sharp NH absorption in IR led us to assign the tetracyclic structure **17** (Scheme III) to this substance. This compound represents the first derivative of the previously unknown 6*H*-oxazolo[5,4-*c*]phenothiazine ring system. It can be isolated in reasonable yield if the initial solution of the monoadduct is allowed to stir at room temperature. TLC monitoring shows that the transformation is slow, requiring 2–3 h for completion. The proposed mechanism for this process assumes that the ortho quinone imine tautomer of **16b** undergoes a proton shift leading to an ortho phenolic Schiff base, which cyclizes in an irreversible fashion to the oxazoline, itself oxidized (by DDQ) to the oxazole **17** (Scheme IV, path B). This cyclization process, highly prominent in the case of the monoadduct **16b**, apparently does not occur in the case of the 1,4-diadduct **14b**. Solutions of the latter are quite stable and no sign of a corresponding tetracyclic structure was ever detected, in spite of the preferred imino structure of the 4-substituent.

II. Preparation and Reactivity of *S*-Oxides of 5*H*-Benzo[*a*]phenothiazin-5-one. Since attempts at direct oxidation of 5*H*-benzo[*a*]phenothiazin-5-one (**3**) to the sulfoxide **4a** or sulfone **4b** also failed to afford any isolable product, the indirect approach described in part I, was again applied (Scheme V). Thus, 5*H*-benzo[*a*]phenothiazin-5-one[13a] (**3**) was reduced to 5-hydroxy-12*H*-benzo[*a*]phenothiazine (**18**), which was acetylated (**19**), oxidized (**20a** and **20b**), and then hydrolyzed in aqueous sodium hydroxide to the required 5-hydroxy-12*H*-benzo[*a*]phenothiazine *S*-oxide (**21a**) and *S,S*-dioxide (**21b**), potential precursors to **4a** and **4b**. As in the case of **2a** and **2b** oxidation experiments revealed that the desired **4a** and **4b** could not be isolated, but their formation in oxidative medium was established via the formation of adducts. Thus oxidation of **21b** with sodium chlorite in aqueous acidic medium led to the formation of the 6-hydroxy derivative **22**.

Addition of amines, such as ammonia, propylamine, and *N*-methylpiperazine, to preformed **4a** or **4b** in THF solution containing excess DDQ leads to monoadducts **23**, **24**, **25** and **26** (Scheme V), resulting from attack of the amine at C-6 followed by reoxidation. These highly colored adducts are easily isolated by crystallization and/or chromatography and are quite stable. Interestingly, in the ^{1}H NMR spectrum ($CDCl_3$) of the propyl amino adduct **25**, coupling of the $NHCH_2$ protons reveals that the substituent, in solution, prefers the amine rather than the imine form.

Scheme V



Conclusion. We have prepared the hitherto unknown sulfoxide (**2a**) and sulfone (**2b**) of 3*H*-phenothiazin-3-one by ring oxidation of 3-hydroxy-10*H*-phenothiazine *S*-oxide (**6a**) and *S,S*-dioxide (**6b**), respectively. The pronounced reactivity of **2a** and **2b** prohibits their isolation but allows their trapping through addition of nucleophiles to the oxidative medium. Thus water, alcohols, and amines (primary and secondary) lead to isolable adducts resulting from initial attack of the nucleophile at the C-4 position of the ring system. Thus, trapping with water leads to 4-hydroxy derivatives **13a** and **13b** while the presence of excess methanol or amines affords 4,4-diadduct **12** and 1,4-diadducts **14a**, **14b** and **15b**, respectively. The monoadducts of alcohols or amines are too reactive to be isolable. However, the monoadduct resulting from trapping preformed **2b** with a stoichiometric quantity of *n*-propylamine slowly rearranges in situ to afford a derivative of the novel 6*H*-oxazolo[5,4-*c*]phenothiazine ring system **17**.

In an analogous fashion, trapping by nucleophiles of the *S*-oxide (**4a**) and *S,S*-dioxide (**4b**) of 5*H*-benzo[*a*]phenothiazin-5-one leads to stable 6-substituted derivatives.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 681 spectrophotometer. Varian EM 390 (90 MHz), Bruker AM 250, and Bruker AM 300 instruments were used to record ^{1}H NMR spectra. Proton chemical shifts are relative to tetramethylsilane (Me_4Si) as internal standard. Mass spectrometric measurements were performed by Morgan Schaffer Corp.,

(17) Pashkevich, T. K.; Afanas'eva, G. B.; Pashkevich, K. I.; Postovskii, I. Ya. *Khim. Geterotsikl. Soedin.* **1975**, *3*, 353; *Chem. Abstr.* **1975**, *83*, 28174X.

Montreal, on a Hitachi-Perkin-Elmer RMU-6D mass spectrophotometer. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, and Galbraith Laboratories, Inc., Knoxville, TN. X-ray diffraction measurements were made on an ENRAF-NONIUS CAD-4 diffractometer.

3*H*-Phenothiazin-3-one (1) and 5*H*-benzo[*a*]phenothiazin-5-one (3) were prepared from 2-aminothiophenol and 1,4-benzoquinone and 1,4-naphthoquinone, respectively, by the improved method developed recently in our laboratories.[13a]

3-Acetoxy-10*H*-phenothiazine (7). A mixture of 3*H*-phenothiazin-3-one (1, 30 g, 0.14 mol), sodium hydrosulfite (60 g), ethyl acetate (500 mL), and water (600 mL) was stirred vigorously at room temperature for 1 h. The yellow-brown organic layer was washed with water, dried over sodium sulfate, and evaporated to dryness. The crude 3-hydroxy-10*H*-phenothiazine (5) was dissolved in pyridine (150 mL) and acetic anhydride (60 mL) was added. After 20 min at room temperature, the mixture was evaporated to dryness, and the residue was slurried with ether and filtered to afford **7** as a tan-colored solid (30.6 g, 84%): mp 193–195 °C; IR (KBr) 3380 (NH) 1745 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.20 (s, 3 H, CH_3), 6.55–7.15 (m, 7 H, Ar), and 8.63 (br s, 1 H, NH, exchangeable). Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.34; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.70; H, 4.71; N, 5.41; S, 12.58.

3-Acetoxy-10*H*-phenothiazine 5-Oxide (8a). To a suspension of **7** (3.85 g, 15 mmol) in methylene chloride (75 mL) was added 85% *m*-chloroperoxybenzoic acid (3.045 g, 15 mmol), and the mixture was stirred at room temperature for 24 h. The insolubles were filtered, stirred in methylene chloride (75 mL) for 1 h, and filtered again. The **8a** obtained as a grayish solid (3.85 g, 94%) was suitable for use in the next step. A sample crystallized from methanol as cream-colored shiny crystals: mp 220 °C dec; IR (KBr) 1770 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 2.30 (s, 3 H, CH_3), 7.10–7.63 (m, 5 H, Ar), 7.72 (d, J = 1 Hz, 1 H, H_4), 7.93 (dd, J = 1 and 5 Hz, 1 H, H_6), and 10.40 (br s, 1 H, NH, exchangeable). Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.13; S, 11.73. Found: C, 61.67; H, 4.14; N, 5.17; S, 11.78.

3-Acetoxy-10*H*-phenothiazine 5,5-Dioxide (8b). A mixture of **7** (28.9 g, 0.112 mol) and 85% *m*-chloroperoxybenzoic acid (87 g, 0.42 mol) in methanol (400 mL) and methylene chloride (400 mL) was refluxed for 20 h. After cooling down and evaporating to one-third of the volume, the suspension was filtered to afford **8b** as a cream-colored solid (21.8 g, 67%) suitable for use in the next step. A sample crystallized from methanol as light yellow crystals: mp 254–256 °C; IR (KBr) 3375 (NH), 1760 (C=O), 1290 (SO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.30 (s, 3 H, CH_3), 7.10–7.74 (m, 5 H, Ar), 7.77 (d, J = 1 Hz, 1 H, H_4), 7.98 (dd, J = 1 and 5 Hz, 1 H, H_6), and 11.10 (br s, NH, exchangeable); mass spectrum, m/e 289 (M^+). Anal. Calcd for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.83; N, 4.84; S, 11.08. Found: C, 58.00; H, 3.90; N, 4.80; S, 11.19.

3-Hydroxy-10*H*-phenothiazine 5-Oxide (6a). To a suspension of **8a** (2.0 g) in methanol (50 mL) was added 2 N aqueous NaOH (20 mL) and a solution rapidly resulted. After being stirred at room temperature for 10 min, the mixture was neutralized with 10% aqueous acetic acid, causing precipitation of **6a** as an off-white solid (970 mg, 51%). Crystallization from methanol afforded cream-colored crystals: mp 234–236 °C (lit.[15b] mp 229–230 °C); IR (KBr) 3600–2800 (NH, OH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.00–7.68 (m, 6 H, Ar), 7.84 (dd, J = 1 and 4.5 Hz, 1 H, H_6), 9.57 and 10.63 (2 br s, 2 H, NH and OH, exchangeables). Anal. Calcd for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.06; S, 13.87. Found: C, 62.41; H, 3.94; N, 6.02; S, 14.04.

3-Hydroxy-10*H*-phenothiazine 5,5-Dioxide (6b). To a suspension of **8b** (20.0 g) in methanol (300 mL) was added 2 N aqueous NaOH (200 mL), and a solution rapidly resulted. After 20 min the mixture was neutralized with 10% aqueous acetic acid (300 mL), causing separation of **6b** as a tan-colored fluffy solid that was filtered (15.3 g, 90%): mp 269–271 °C (lit.[15a] mp 266–267 °C); IR (KBr) 3600–3100 (br, NH, OH), 1260, 1130 (SO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.03–7.72 (m, 6 H, Ar), 7.87 (dd, J = 1 and 5 Hz, 1 H, H_6), 9.80 and 10.50 (2 br s, 2 H, NH and OH, exchangeable); ^1H NMR (300 MHz, THF-d_8) δ 6.97 (dd, J = 2.5 and 8.5 Hz, 1 H, H_2), 7.03 (d, J = 8.5 Hz, 1 H, H_1), 7.08 (m, 2 H, H_7, H_9), 7.43 (m, 1 H, H_8), 7.86 (dd, J = 1.4 and 8.4 Hz, 1 H, H_6), 8.63 and 9.50 (2 s, 2 H, NH and OH, exchangeable). Anal. Calcd for $C_{12}H_9NO_3S$: C, 58.28; H, 3.67; N, 5.67; S, 12.97. Found: C, 58.14; H, 3.69; N, 5.68; S, 13.09.

4-Chloro-3-hydroxy-10*H*-phenothiazine 5,5-Dioxide (9b). Following the same step procedure as for the preparation of **6b**, but using 4-chloro-3*H*-phenothiazin-3-one[18] as starting material, **9b** was obtained as a colorless, light-sensitive solid: mp 286 °C dec; IR (KBr) 3305 (NH), 3500–3000 (br, OH), 1138 (SO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.90–7.35 (m, 5 H, 4 aromatic + 1 exchangeable), 7.50 (m, 1 H, aromatic), 7.82 (dd, J = 1 and 8 Hz, 1 H, H_6), 10.55 (br s, 1 H, exchangeable). Anal. Calcd for $C_{12}H_8ClNO_3S$: C, 51.16; H, 2.86; N, 4.97; S, 11.38; Cl, 12.59. Found: C, 51.24; H, 3.06; N, 4.95; S, 11.57; Cl, 12.69.

3-Oxo-3*H*-phenothiazine 5,5-Dioxide (2b). In Situ Characterization. To a solution of **6b** (13 mg) in THF-d_8 (1 mL) was added DDQ (15 mg), and a 300-MHz ^1H NMR of the mixture was run. Although a little **6b** remained, strong signals corresponding to **2b** were observed: δ 6.70 (dd, J = 2 and 10 Hz, 1 H, H_2), 7.34 (d, J = 2 Hz, 1 H, H_4), 7.43 (d, J = 10 Hz, 1 H, H_1), 7.67 and 7.79 (2 dt, J = 1.4 and 7.6 Hz, 2 H, H_7 and H_8), 7.87 (dd, J = 1.4 and 7.6 Hz, 1 H, H_9), and 8.09 (dd, J = 1.3 and 7.6 Hz, 1 H, H_6).

4-Hydroxy-3-oxo-3*H*-phenothiazine 5-Oxide (13a). The process, described below for the preparation of **13b**, using **6a** as starting material, afforded **13a** as a dark red solid (68%): mp 245 °C dec; IR (KBr) 3600–2800 (br, OH) 1695 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.76 (d, J = 7 Hz, 1 H, H_2), 7.29–7.90 (m, 4 H, Ar), 8.05 (dd, J = 0.5 and 5 Hz, 1 H, H_6), and 12.60 (br s, OH, exchangeable). Anal. Calcd for $C_{12}H_7NO_3S$: C, 58.76; H, 2.88; N, 5.71; S, 13.07. Found: C, 58.41; H, 2.82; N, 5.49; S, 13.42.

4-Hydroxy-3-oxo-3*H*-phenothiazine 5,5-Dioxide (13b). To a suspension of **6b** (1.75 g, 7 mmol) in 2% aqueous sulfuric acid (25 mL) was added, at room temperature, a solution of 80% sodium chlorite (3.17 g, 28 mmol) in water (25 mL). The mixture was stirred for 15 min and the red-orange precipitate was filtered to afford crude product **13b** (1.73 g). Purification was achieved by crystallization from DMF–methanol: mp 266 °C dec; IR (KBr) 3600–2900 (br, OH) 1698 (C=O), 1630 (C=C), 1145, and 1315 (SO_2) cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6) δ 6.77 (d, J = 10.3 Hz, 1 H, H_2), 7.30 (d, J = 10.3 Hz, 1 H, H_1), 7.52 (m, 2 H, H_7 and H_9), 7.75 (m, 1 H, H_8), 8.00 (m, 1 H, H_6), 12.39 (br s, OH); assignments done via decoupling experiments. Anal. Calcd for $C_{12}H_7NO_4S$: C, 55.15; H, 2.70; N, 5.36; S, 12.27. Found: C, 54.76; H, 2.96; N, 5.38; S, 12.30.

Sodium Chlorite Oxidation of 9b. When the above process was applied to **9b**, a red-orange precipitate was obtained whose spectral data (IR, NMR) were identical with those of **13b**.

3,4-Dihydroxy-10*H*-phenothiazine 5,5-Dioxide. To a suspension of 4-hydroxy-3-oxo-3*H*-phenothiazine 5,5-dioxide (**13b**, 0.8 g) in a mixture of water (20 mL) and ethyl acetate (20 mL) was added sodium hydrosulfite (2 g), and the resulting mixture was stirred at room temperature for 20 min. The insoluble solid was then filtered, washed with water, and dried to afford the title product as a colorless solid (412 mg): mp 261 °C dec; IR (KBr) 3600–3000 (br s, 2 OH, NH) 1330, 1125 (SO_2) cm^{-1}; ^1H NMR (DMF-d_7) δ 6.60 (d, J = 6 Hz, 1 H, H_2), 6.93–7.55 (m, 4 H, Ar), 7.83 (dd, J = 1 and 6 Hz, 1 H, H_6), 9.60 and 10.33 (2 br s, 2 OH and NH, exchangeable). Anal. Calcd for $C_{12}H_9NO_4S$: C, 54.74; H, 3.45; N, 5.32; S, 12.18. Found: C, 54.85; H, 3.54; N, 5.26; S, 12.11.

4,4-Dimethoxy-3,4-dihydro-3-oxo-10*H*-phenothiazine 5,5-Dioxide (12). To a suspension of **6b** (247 mg, 1 mmol) in methanol (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 579 mg, 2.5 mmol), and the mixture was stirred at room temperature. A green solution formed which after a few minutes began to deposit a yellow crystalline solid. After 2 h this was filtered to afford **12** (182 mg, 59%), mp 212 °C dec, with previous color change to red starting from 60 °C: IR (KBr) 3290 (NH), 1690 (C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6) δ 3.25 (s, 6 H, $(OCH_3)_2$), 6.51 (d, J = 10 Hz, 1 H, H_2), 7.24 (d, J = 10 Hz, 1 H, H_1), 7.38 (m, 2 H, H_7, H_9), 7.67 (m, 1 H, H_8), 7.86 (dd, J = 1.5 and 8.5 Hz, 1 H, H_6), and 11.40 (br s, NH, exchangeable); ^{13}C NMR (75 MHz, Me_2SO-d_6) δ 51.72 (OCH_3), 96.10, 105.89, 117.88, 121.80, 124.47, 124.99, 129.79, 132.59, 135.81, 137.51, 139.13, 193.02 (C=O).

(18) Terdic, M.; Bodea, C. *Rev. Roum. Chim.* **1968**, *13*, 1241.

This product on standing in air changed into a red-orange solid which was identical with **13b**. Even samples kept in closed vials became red and thus no elemental analysis could be obtained.

1-(Propylamino)-4-(propylimino)-3,4-dihydro-3-oxo-10*H*-phenothiazine 5-Oxide (14a). With the same procedure as for **14b** below, but with **6a** as starting material, **14a** was obtained as a brick-red solid: mp 172 °C dec; IR (KBr) 3300–3100 (2 NH) 1575 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (2 t, 6 H, $2CH_3$), 1.75 (m, 4 H, $2CH_2$), 3.23 (q, 2 H, CH_2NH, collapses to t, J = 4.5 Hz on D_2O exchange), 3.80 (m, 2 H, CH_2N), 5.56 (s, 1 H, H_2), 7.32–7.72 (m, 3 H, Ar), 7.88 (dd, J = 0.5 and 4 Hz, 1 H, H_6), 7.90 and 8.10 (2 br s, 2 H, 2 NH, exchangeable). Anal. Calcd for $C_{18}H_{21}N_3O_2S$: C, 62.95; H, 6.16; N, 12.23; S, 9.34. Found: C, 63.05; H, 6.42; N, 12.03; S, 9.39.

1-(Propylamino)-4-(propylimino)-3,4-dihydro-3-oxo-10*H*-phenothiazine 5,5-Dioxide (14b). To a solution of **6b** (247 mg, 1 mmol) in THF (10 mL) was added at room temperature DDQ (765 mg, 3.3 mmol). The resulting dark solution was stirred for 2 min and *n*-propylamine (590 mg, 10 mmol) was added rapidly. The mixture became dark red and rapidly a yellow solid separated out of solution as the mixture warmed up slightly. After being stirred for 15 min, the mixture was filtered and the dark red residue from evaporation of the filtrate was chromatographed on silica gel, eluting with a 1:19 mixture of ethyl acetate and toluene, to afford 270 mg (75%) of **16b** as a dark red solid. Crystallization from methanol afforded red-purple crystals: mp 174–176 °C; IR (KBr) 3350–3050 (br, 2 NH) 1575 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87–1.23 (m, 6 H, 2 CH_3), 1.59–2.03 (m, 4 H, 2 CH_2), 3.23 (q, J = 4 Hz, 2 H, CH_2N, collapses to t on D_2O exchange), 3.92 (m, 3 H, CH_2N and NH exchangeable), 5.67 (s, 1 H, H_2), 7.34–7.68 (m, 3 H, Ar), 7.96 (br s, 1 H, NH, exchangeable), and 8.10 (dd, J = 1 and 5 Hz, 1 H, H_6); mass spectrum, m/e 359 (M^+). Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.14; H, 5.89; N, 11.69; S, 8.92. Found: C, 60.08; H, 5.93; N, 11.80; S, 8.71.

X-ray Crystal Structue Analysis of 14b. Suitable crystals of **14b** ($C_{18}H_{21}N_3O_3S$) for X-ray diffraction studies formed from methanol with space group symmetry of $P2_1/c$ and cell constants of a = 11.793 (7) Å, b = 14.426 (8) Å, c = 11.257 (5) Å, and β = 112.23 (5)° for Z = 4 and a calculated density of 1.347 g/cm^3. Of the 2443 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 1379 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[19] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. Because the structure appears to be a combination of two tautomers the protons observed in Fourier difference maps attached to N10 and N16 were assigned occupancies of 0.5. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.106. No abnormally short intermolecular contacts were noted. Tables I, II, and III containing the final fractional coordinated, temperature parameters, bond distances and bond angles are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **14b** from the final X-ray coordinates.

1,4-Bis(4-methylpiperazin-1-yl)-3-oxo-3*H*-phenothiazine 5,5-Dioxide (15b). To a solution of **6b** (494 mg, 2 mmol) in THF (40 mL) was added DDQ (1.5 g, 6.6 mmol), and the mixture was stirred at room temperature. After 5 min *N*-methylpiperazine (2.0 g, 20 mmol) was rapidly added and the mixture became a dark red suspension. The reaction was slightly exothermic. After stirring for 30 min, the insoluble yellow complex was filtered and the filtrate evaporated to dryness. The dark residue was crystallized from a mixture of toluene and hexane to afford **15b** as red microcrystals (495 mg, 56%): mp 247–249 °C dec; IR (KBr) 1560 (C=O), 1500 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 and 2.38 (s, 6 H, $2CH_3$) 2.63 (m, 8 H, CH_2NCH_3), 3.72 (t, J = 3 Hz, 4 H, CH_2N), 4.32 (t, J = 3 Hz, 4 H, CH_2N), 5.51 (s, 1 H, H_2), 7.35–7.65 (m, 3 H, Ar), and 8.06 (dd, J = 0.5 and 4 Hz, 1 H, H_6). Anal. Calcd for $C_{22}H_{27}N_5O_3S$: C, 59.84; H, 6.16; N, 15.86; S, 7.26. Found: C, 59.98; H, 6.35; N, 15.58; S, 7.11.

2-Ethyl-6*H*-oxazolo[5,4-*c*]phenothiazine 11,11-Dioxide (17). To a solution of **6b** (247 mg, 1 mmol) in THF (10 mL) was added DDQ (811 mg, 3.5 mmol) at room temperature, and a dark green solution resulted, which was stirred for 5 min. A solution of *n*-propylamine (75 mg, 1.25 mmol) in THF (1 mL) was then added, causing the appearance of a dark red coloration. Stirring was continued for 2.5 h, then the mixture was evaporated to dryness, and the residue was stirred in CH_2Cl_2 (20 mL) for 10 min and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel, eluting with a 1:4 mixture of acetone and CH_2Cl_2, to afford **17** (193 mg, 64%) as a cream-colored solid. Crystallization from THF affords cream-colored microneedles: mp 295–298 °C; IR (KBr) 3285 (NH) 1480 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.30 (t, J = 5 Hz, 3 H, CH_3), 2.98 (q, J = 5 Hz, 2 H, CH_2), 7.08–7.38 (m, 3 H, H_2, H_8, and H_9), 7.59 (m, 1 H, H_7), 7.90 (dd, J = 0.5 and 6 Hz, 1 H, H_6), 7.92 (d, J = 6 Hz, 1 H, H_1); mass spectrum, m/e 300 (M^+). Anal. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.03; N, 9.33; S, 10.68. Found C, 59.98; H, 4.37; N, 8.97; S, 10.80.

5-Hydroxy- and 5-Acetoxy-12*H*-benzo[*a*]phenothiazine (18 and 19). To a suspension of **3**[13a] (50 g, 0.19 mol) in DMF (500 mL) was added a solution of sodium hydrosulfite (66 g, 0.38 mol) in water (300 mL). The mixture was stirred under an inert atmosphere for 3 h, it was poured onto water (2 L), and after 15 min of vigorous stirring the yellow insolubles were filtered and washed copiously with water, then with hexane, while avoiding contact with air. The solid was then stirred in methylene chloride (250 mL) for a few minutes and filtered again. The crude **18** thus obtained (35 g) was immediately suspended in pyridine (50 mL) and acetic anhydride (27 mL) was rapidly added. A dark solution resulted and the mixture became warm. The reaction was allowed to proceed without cooling for 1 h, whereupon solids had separated out. Ether (300 mL) was added and after 20 min of further stirring, the mixture was filtered to afford **19** (18.6 g) as a greenish yellow solid. Crystallization from ethyl acetate afforded yellow crystals, mp 185–186 °C [Solutions should be protected from light which causes polymerization.]; IR (KBr) 3420 (NH), 1745 (C=O), 1210 (C—O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.40 (s, 3 H, CH_3), 6.70–7.28 (m, 4 H, aromatic), 6.96 (s, 1 H, H_6), 7.40–7.91 (m, 3 H, aromatic), 8.41 (m, 1 H, aromatic), 8.68 (br s, 1 H, NH, exchangeable). Anal. Calcd for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.44; H, 4.10; N, 4.60; S, 10.28.

5-Acetoxy-12*H*-benzo[*a*]phenothiazine 7-Oxide (20a). To a suspension of **19** (10 g, 32.5 mmol) in methylene chloride (125 mL) was added a solution of 85% *m*-chloroperoxybenzoic acid (6.61 g, 32.5 mmol) in methanol (125 mL). A reddish solution resulted which was stirred at ambient temperature for 1.5 h. The product that had slowly crystallized was filtered and washed with methylene chloride to afford **20a** as a cream-colored solid (8.76 g): mp 179–181 °C; IR (KBr) 3250 (br, NH), 1770 (C=O), 1200 (C—O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.53 (s, 3 H, CH_3), 6.74 (m, 1 H, aromatic), 6.90 (m, 2 H, aromatic), 7.38–7.78 (m, 4 H, aromatic), 7.62 (s, 1 H, H_6), 8.02 (d, J = 5 Hz, 1 H, H_8), and 10.80 (s, 1 H, NH, exchangeable). Anal. Calcd for $C_{18}H_{13}NO_3S$: C, 66.85; H, 4.05; N, 4.33; S, 9.92. Found: C, 66.79; H, 4.08; N, 4.06;, S, 9.74.

5-Acetoxy-12*H*-benzo[*a*]phenothiazine 7,7-Dioxide (20b). To a suspension of **19** (10 g, 32.5 mmol) in CH_2Cl_2 (125 mL) was added a solution of 85% *m*-chloroperoxybenzoic acid (18 g, 88.7 mmol) in methanol (125 mL). All solids dissolved to give a red solution which rapidly became a suspension. The mixture was refluxed for 2.5 h, as the solid dissolved and new solids separated. After cooling to room temperature, these solids were filtered, affording a mixture of **20b** and *m*-chlorobenzoic acid. Crystallization from THF afforded **20b** (4.33 g, 39%) as fluffy cream-colored needles: mp 284–287 °C; IR (KBr) 3390 (NH), 1760 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.34 (s, 3 H, CH_3), 7.28 (m, 1 H, aromatic), 7.50–8.05 (m, 6 H, aromatic), 7.70 (s, 1 H, H_6), 8.82 (m, 1 H, H_8), and 10.80 (br s, NH, exchangeable). Anal. Calcd for $C_{18}H_{13}NO_4S$: C, 63.70; H, 3.86; N, 4.13; S, 9.45. Found: C, 63.67; H, 3.82; N, 4.20; S, 9.44.

5-Hydroxy-12*H*-benzo[*a*]phenothiazine 7-Oxide (21a). To a suspension of **20a** (5 g) in methanol (120 mL), kept under nitrogen atmosphere, was added 2 N aqueous NaOH solution (100 mL) rapidly, and the mixture was stirred well for 5 min, resulting

(19) The following library of crystallographic programs was used: MULTAN 80, P. Main, University of York, York, England, 1980; ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN, 1970; SDP Plus V1.1, Y. Okaya and B. A. Frenz, B. A. Frenz and associates, College Station, TX, 1984.

in a slightly cloudy solution. Quenching with 10% aqueous acetic acid (110 mL) led to precipitation of crude **21a** as a reddish solid which was filtered. It was stirred in methylene chloride (50 mL) overnight and filtered again to afford purified product (2.9 g) as a pink solid, mp 210 °C dec, having very low solubility in most organic solvents: IR (KBr) 3600–2900 (br s, NH and OH), 1590 (C=C) cm^{-1}; ^1H NMR (250 MHz, Me_2SO-d_6) δ 7.19 (s, 1 H, H_6), 7.23 (m, 1 H, aromatic), 7.63–7.94 (m, 5 H, aromatic), 8.29 (m, 1 H, aromatic), 8.83 (d, J = 5 Hz, 1 H, H_8), 10.27 and 10.68 (2 s, 2 H, NH and OH, exchangeable). Anal. Calcd for $C_{16}H_{11}NO_2S$: C, 68.30; H, 3.94; N, 4.98; S, 11.40. Found: C, 67.98; H, 3.71; N, 4.81; S, 11.52.

5-Hydroxy-12*H*-benzo[*a*]phenothiazine 7,7-Dioxide (21b). A suspension of **20b** (6.6 g) in methanol (200 mL) was stirred under a nitrogen flow for 5 min to purge out oxygen. A 2 N aqueous NaOH solution (132 mL) was then added, and the solids were dissolved to give a yellow solution, which was stirred at room temperature for 7 min and then quenched with 10% aqueous acetic acid (200 mL). The resulting light orange precipitate was filtered to afford crude **21b** (5.68 g, 98%). Crystallization of a sample from THF afforded light pink microcrystals: mp 334 °C dec; IR (KBr) 3400 (OH), 3365 (NH), 1245 (SO_2) cm^{-1}; ^1H NMR (250 MHz, Me_2SO-d_6) δ 7.22 (s, 1 H, H_6), 7.29 (m, 1 H, aromatic), 7.62–7.97 (m, 5 H, aromatic), 8.32 (d, J = 5 Hz, 1 H, aromatic), 8.80 (d, J = 4 Hz, 1 H, H_8), 10.58 (s, 2 H, NH and OH, exchangeable). Anal. Calcd for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71, S, 10.79. Found: C, 64.93; H, 4.00; N, 4.71; S, 10.68.

6-Hydroxy-5-oxo-5*H*-benzo[*a*]phenothiazine 7,7-Dioxide (22). To a suspension of **21b** (297 mg, 1 mmol) in 2% aqueous sulfuric acid (8 mL) was slowly added 80% sodium chlorite (452 mg, 4 mmol), and the frothing mixture was stirred at room temperature for 45 min. The insoluble yellow-orange solid which resulted was filtered and washed with water to afford **22** (260 mg, 83%): mp 330 °C; IR (KBr) 3600–3000 (br s, OH) 1705 (C=O), 1290, and 1130 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMF-d_7, 77 °C) δ 7.47 (t, 1 H, aromatic), 7.68 (t, 1 H, aromatic), 7.77 (t, 1 H, aromatic), 7.90 (m, 3 H, aromatic), 8.11 (d, J = 7.5 Hz, 1 H, H_4), and 8.67 (d, J = 8 Hz, 1 H, H_8). Anal. Calcd for $C_{16}H_9NO_4S$: C, 61.73; H, 2.91; N, 4.50; S, 10.30. Found: C, 61.61; H, 3.18; N, 4.42; S, 10.47.

6-Amino-5-oxo-5*H*-benzo[*a*]phenothiazine 7,7-Dioxide (23). To a suspension of **21b** (297 mg, 1 mmol) in THF (20 mL) was added DDQ (500 mg, 2.2 mmol), and the solids were rapidly dissolved to give a dark greenish solution which was stirred for 5 min. Gaseous ammonia was then bubbled through the mixture for a few minutes, and the resulting suspension was diluted with THF and filtered. The orange residue obtained on evaporation of the filtrate was crystallized from toluene to afford **23** as a fluffy orange solid (211 mg, 68%): mp 265–267 °C; IR (KBr) 3400, 3310 (NH_2), 1690 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.45–8.20 (m, 7 H, Ar), 8.41 (br s, 2 H, NH_2, exchangeable), and 8.62 (dd, J = 0.5 and 5 Hz, 1 H, H_8); mass spectrum, m/e 310 (M^+). Anal. Calcd for $C_{16}H_{10}N_2O_3S$: C, 61.92; H, 3.25; N, 9.03; S, 10.33. Found: C, 61.89; H, 3.09; N, 9.01; S, 10.24.

6-(Propylamino)-5-oxo-5*H*-benzo[*a*]phenothiazine 7-Oxide (24). To a suspension of **21a** (562 mg, 2 mmol) in THF (15 mL) were added DDQ (1.02 g, 4.5 mmol) and 10 min later *n*-propylamine (295 mg, 5 mmol). The resulting dark red mixture was stirred at ambient temperature for 30 min; then it was filtered and the filtrate was evaporated to dryness. The residue was stirred in a mixture of water (15 mL) and ethyl acetate (15 mL) for 5 min and filtered again. The brick-red solid was then chromatographed on a column of silica gel which was eluted with a mixture of acetone and methylene chloride (1:3) to afford **24** as a brick-colored solid (356 mg, 53%): mp 141 °C dec; IR (KBr) 3285 (NH), 1670 (C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (t, J = 5 Hz, 3 H, CH_3), 1.94 (m, 2 H, CH_2), 3.73 and 4.06 (2 m, 2 H, CH_2N), 7.12 (br s, 1 H, NH), 7.42–7.92 (m, 6 H, Ar), 8.16 (d, J = 8 Hz, 1 H, H_4), and 8.78 (d, J = 8 Hz, 1 H, H_8). Anal. Calcd for $C_{19}H_{16}N_2O_2S$: C, 67.83; H, 4.79; N, 8.33; S, 9.53. Found: C, 67.65; H, 5.08; N, 8.15; S, 9.20.

6-(Propylamino)-5-oxo-5*H*-benzo[*a*]phenothiazine 7,7-Dioxide (25). To a suspension of **21b** (594 mg, 2 mmol) in THF (10 mL) was added DDQ (1.02 g, 4.5 mmol) at room temperature, and a dark green solution resulted. After being stirred for 2 min, *n*-propylamine (148 mg, 2.5 mmol) was added and the mixture became dark red. Stirring was continued for another 30 min, the mixture was evaporated to dryness, and the residue was stirred with CH_2Cl_2 (50 mL) for 15 min and filtered. The residue obtained on evaporation of the filtrate was crystallized from a mixture of toluene and hexane to afford **25** (442 mg, 63%) as a red-brown crystalline solid: mp 149–151 °C dec; IR (KBr) 3240 (NH), 1675 (C=O), 1270 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, J = 5 Hz, 3 H, CH_3), 1.83 (m, 2 H, CH_2), 3.97 (q, 2 H, CH_2N, collapses to t on D_2O exchange, J = 5 Hz), 7.30–8.20 (m, 7 H, Ar), and 8.70 (dd, J = 0.5 and 5 Hz, 1 H, H_8). Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.75; H, 4.58; N, 7.95; S, 9.10. Found: C, 64.66; H, 4.48; N, 7.95; S, 9.04.

6-(4-Methylpiperazin-1-yl)-5-oxo-5*H*-benzo[*a*]phenothiazine 7,7-Dioxide (26). To a suspension of **21b** (891 mg, 3 mmol) in THF (20 mL) was added DDQ (1.5 g, 6.5 mmol) at room temperature. The resulting dark green solution was stirred for 5 min; then *N*-methylpiperazine (350 mg, 3.5 mmol) was added, causing the appearance of a dark red color and separation of solids. After 15 min more *N*-methylpiperazine (350 mg) was added, and 15 min later the mixture was evaporated to dryness. The residue was stirred in CH_2Cl_2 (50 mL) for 10 min and filtered. The filtrate was evaporated to dryness and the residual dark red solid crystallized from a mixture of toluene and hexane to afford **26** (740 mg, 63%) as red-brown needles: mp 183 °C dec; IR (KBr) 1670 (C=O), 1280 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H, CH_3), 2.63 (t, distorted, 4 H, $(CH_2)_2NCH_3$), 4.20 (t, distorted, 4 H, $(CH_2)_2N$), 7.17–8.12 (m, 7 H, Ar), and 8.45 (dd, J = 0.5 and 5 Hz, 1 H, H_8). Anal. Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.10; H, 4.87; N, 10.68; S, 8.15. Found: C, 63.89; H, 4.90; N, 10.56; S, 8.10.

Acknowledgment. We extend our appreciation to Dr. J. G. Atkinson for helpful discussion in the preparation of this manuscript and to Dr. M. A. Bernstein for his collaboration in the obtainment of NMR data.

Registry No. 1, 581-30-6; **2a**, 109433-78-5; **2b**, 109433-79-6; **3**, 25947-04-0; **4a**, 93244-67-8; **4b**, 93244-68-9; **5**, 1927-44-2; **6a**, 38015-17-7; **6b**, 37537-64-7; **7**, 99525-91-4; **8a**, 99525-81-2; **8b**, 99525-82-3; **9b**, 99525-84-5; **12**, 109433-80-9; **13a**, 109433-81-0; **13b**, 93211-57-5; **14a**, 109433-82-1; **14b**, 109433-83-2; **15b**, 93211-72-4; **17**, 109433-84-3; **18**, 20349-55-7; **19**, 93211-73-5; **20a**, 96839-83-7; **20b**, 93211-74-6; **21a**, 96839-89-3; **21b**, 93211-75-7; **22**, 93244-59-8; **23**, 93211-78-0; **24**, 109433-85-4; **25**, 93211-76-8; **26**, 93211-77-9; 4-chloro-3*H*-phenothiazin-3-one, 19601-83-3; *N*-methylpiperazine, 109-01-3; 3,4-dihydroxy-10*H*-phenothiazine 5,5-dioxide, 99525-46-9.

Supplementary Material Available: Computer-generated drawing and tables of the atomic positional and thermal parameters, bond distances, and bond angles for **14b** (5 pages). Ordering information is given on any current masthead page.