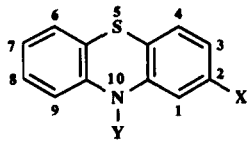
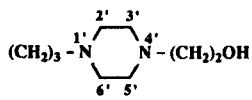
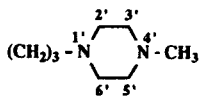
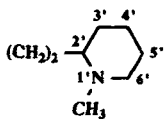
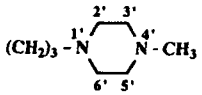
Synthesis of the *N*-Oxides of Phenothiazine Antipsychotic Agents

T. J. JAWORSKI*, M. S. SARDESSAI*, M. ARAVAGIRI‡, G. LIN*, Y. Y. SHI*, E. M. HAWES*x, J. W. HUBBARD*, G. MCKAY*, AND K. K. MIDHA*

Received January 7, 1992, from the *College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0, and the ‡Brentwood Veterans Administration, Building 210, #4, 11301 Wilshire Boulevard, Los Angeles, CA 90073. Accepted for publication August 23, 1992.

Abstract □ Chlorpromazine *N*-oxide, fluphenazine $N^{4'}$-oxide, prochlorperazine $N^{4'}$-oxide, sulforidazine *N*-oxide, and trifluoperazine $N^{4'}$-oxide were synthesized by oxidation of the designated nitrogen atom in the *N*-10 side chain of the respective parent drug with 3-chloroperoxybenzoic acid. In the case of trifluoperazine, a stepwise increase in the amount of oxidant yielded the $N^{1'},N^{4'}$-dioxide and $N^{1'},N^{4'},S$-trioxide. The *N*',*S*-dioxides of chlorpromazine and sulforidazine were obtained by hydrogen peroxide oxidation of the appropriate parent drug.



Compound (number)	X	Y
Chlorpromazine (1a)	Cl	$(CH_2)_3N(CH_3)_2$
Fluphenazine (2a)	CF_3	
Prochlorperazine (3a)	Cl	
Sulforidazine (4a)	SO_2CH_3	
Trifluoperazine (5a)	CF_3	

It is well established that *N*-oxidation of the aliphatic tertiary amine group(s) in the *N*-10 side chain of phenothiazine antipsychotic agents is a major route of metabolism of these drugs in humans.[1] High plasma levels of *N*-oxide metabolites have been observed in humans for chlorpromazine,[2] fluphenazine,[3,4] and trifluoperazine.[5] However, the true contribution of these metabolites to the clinical response has been investigated only in the case of fluphenazine.[4] Fluphenazine $N^{4'}$-oxide was more strongly associated with side effects than was the parent drug. The antidopaminergic activity of *N*-oxide metabolites that have been tested is present when the *N*-oxide moiety is not three carbon atoms distant from the phenothiazine ring.[6] Thus, in vitro pharmacological tests have demonstrated that the $N^{4'}$-oxides of fluphenazine and trifluoperazine possess antidopaminergic activity, whereas chlorpromazine *N*-oxide was devoid of this activity (see structures). Nevertheless, chlorpromazine *N*-oxide is converted to chlorpromazine in humans, and its metabolic profile is very similar to that of the parent drug.[7,8]

There are various reports to the biochemical[9] and chemical[10–17] methods of synthesis of the *N*-oxide metabolites of phenothiazine antipsychotic agents. Generally, the most convenient approach involves the direct chemical oxidation of the tertiary amine group of the drug. Various oxidizing agents have been utilized in these published methods.

Samples of the *N*-oxides of various phenothiazine antipsychotic agents were required for ongoing studies in humans and animals that involved their identification as metabolites,[18] analysis in body fluids,[2–5,19] and metabolism upon dosing of the *N*-oxide itself.[7,8,20,21] Specifically, samples of the *N*-oxides of chlorpromazine (**1a**), fluphenazine (**2a**), prochlorperazine (**3a**), sulforidazine (**4a**), and trifluoperazine (**5a**) were required; procedures for the chemical synthesis have been reported for only the first two cases.[11,12,14–16] Various oxidizing agents were examined in the present work with a view to develop a general procedure for the chemical synthesis of the *N*-oxide metabolites of phenothiazine antipsychotic agents.

Experimental Section

Materials and Reagents—Pure samples of the following drugs were generously supplied by the pharmaceutical company indicated in parentheses: chlorpromazine hydrochloride (Rhône-Poulenc Pharma Inc., Montreal, Quebec, Canada), fluphenazine dihydrochloride (Cord Laboratories, Broomfield, CO), prochlorperazine dimaleate and trifluoperazine dihydrochloride (Smith, Kline and French Laboratories, Philadelphia, PA), and sulforidazine (Sandoz Inc., East Hanover, NJ). All other chemicals were purchased from Aldrich Chemical Company (Milwaukee, WI) or BDH Inc. (Toronto, Ontario, Canada). All drugs obtained as salts were converted to their respective free bases before use.

Instrumentation—Melting points were taken in open gas capillary tubes with a Gallenkamp melting point apparatus and are reported uncorrected. Thin-layer chromatography was carried out on aluminum sheets that were precoated (0.2 mm) with silica gel either with or without a fluorescent indicator (E. Merck, purchased from Terochem Laboratories Ltd., Edmonton, Alberta, Canada), and spots were examined under UV light (254 or 365 nm). The ^{1}H NMR spectra were

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taken on a Bruker AM-300 spectrometer. Chemical shifts were recorded in parts per million downfield from Me_4Si. Fast atom bombardment mass spectra (FAB MS) were obtained in the positive ion mode on a VG 7070 HE double-focusing mass spectrometer operated at a resolution of 1500 under the following operating conditions: argon atom beam; gun emission, 1.2 mA; 7 kV; source pressure, 3×10^{-5} mbar; ambient source temperature; glycerol matrix (with 0.24 N HCl added to aid dissolution where necessary). Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer.

Chlorpromazine *N*-Oxide Maleate (1b)[22]—To a solution of **1a** (1.00 g, 3.13 mmol) in tetrahydrofuran (10 mL; purified according to the literature[23]) at −70 °C was added 3-chloroperoxybenzoic acid (0.65 g, 3.76 mmol; purified according to the literature[24]). After the reaction mixture was stirred for 30 min, it was treated with diethylamine (0.39 mL, 3.76 mmol) for 10 min to destroy the excess 3-chloroperoxybenzoic acid. The reaction mixture was slowly brought to room temperature after which the solvent was removed on a rotavapor. The crude product was purified by column chromatography over silica gel (60–200 mesh) with a mixture of benzene, methanol, and diethylamine (7.5:1.5:1.0) as eluant. The appropriate fraction was collected, and the solvent was removed on a rotavapor. The residue was taken up in dichloromethane (2 mL) and filtered, and the solvent was removed on a rotavapor. The residue was dissolved in dry methanol (10 mL; dried over type 4A molecular sieves) and treated with a solution of maleic acid (0.36 g, 3.13 mmol) in methanol (5 mL) at 4 °C for 8 h. The resultant solid was filtered and washed with methanol (cooled to −20 °C) to give the maleate salt **1b** (0.95 g, 67%) as pale yellow crystals, mp 143–144 °C; ^{1}H NMR (free base, CD_3OD): δ 7.96–7.27 (m, 7H, aromatic H_7), 4.49 (t, 2H, J = 7.3 Hz, CH_2-phenothiazine), 3.37 (t, 2H, J = 7.9 Hz, CH_2-N(O)), 3.08 and 3.06 (two s, 6H, $(CH_3)_2$N(O)), 2.39 (quintet, 2H, J = 7.7 Hz, $CH_2CH_2CH_2$); FAB MS: *m/z* (relative intensity %) 335/337 (MH^+, 26/10).

Anal.—Calcd for $C_{21}H_{23}ClN_2O_5S$: C, 55.93; H, 5.14; N, 6.21. Found: C, 55.97; H, 5.00; N, 6.20.

Fluphenazine $N^{4'}$-Oxide (2b)[25]—This was prepared from **2a** by the same method as described for **1b**. The residue obtained subsequent to column chromatography was recrystallized from acetone to give the *N*-oxide **2b** (45%) as white crystals, mp 144–146 °C; ^{1}H NMR (CD_3OD): 7.27–6.94 (m, 7H, aromatic H_7), 4.06 (m, 2H, CH_2-phenothiazine), 4.02 (m, 2H, CH_2-O), 3.34–3.17 (m, 6H, piperazine $C_{3'}$-H_2, piperazine $C_{5'}$-H_2,CH_2CH_2O), 2.80 (m, 2H, piperazine $C_{2'}$-*He*, piperazine $C_{6'}$-*He*), 2.76 (m, 2H, piperazine $C_{2'}$-*Ha*, piperazine $C_{6'}$-*Ha*), 2.58 (t, 2H, J = 6.9 Hz, acyclic CH_2-$N^{1'}$), 1.92 (quintet, 2H, J = 6.7 Hz, $CH_2CH_2CH_2$); FAB MS: *m/z* (relative intensity %) 454 (MH^+, 75).

Anal.—Calcd for $C_{22}H_{26}F_3N_3O_2S$: C, 58.26; H, 5.78; N, 9.27. Found: C, 57.96; H, 5.74; N, 9.33.

Prochlorperazine $N^{4'}$-Oxide Dimaleate (3b)—This was prepared from **3a** by the same method as described for **1b**. The $N^{4'}$-oxide maleate **3b** was obtained (55%) as cream-colored crystals, mp 173–175 °C; ^{1}H NMR (free base, $CDCl_3$): 7.15–6.82 (m, 7H, aromatic H_7), 3.89 (t, 2H, J = 6.6 Hz, CH_2-phenothiazine), 3.17 (m, 7H, CH_3-N(O), piperazine $C_{3'}$-H_2, piperazine $C_{5'}$-H_2), 2.97 (m, 2H, piperazine $C_{2'}$-*He*, piperazine $C_{6'}$-*He*), 2.56 (m, 4H, acyclic CH_2-$N^{1'}$, piperazine $C_{2'}$-*Ha*, piperazine $C_{6'}$-*Ha*), 1.89 (quintet, 2H, J = 6.7 Hz, $CH_2CH_2CH_2$); FAB MS: *m/z* (relative intensity %) 390/392 (MH^+, 62/26).

Anal.—Calcd for $C_{28}H_{32}ClN_3O_9S$: C, 54.06; H, 5.18; N, 6.75. Found: C, 53.84; H, 5.36; N, 6.45.

Sulforidazine *N*-Oxide (4b)—This was prepared from **4a** by the same method as described for **1b** except that a reaction time of 20 min was employed. The residue obtained subsequent to column chromatography was recrystallized from acetone to give the *N*-oxide **4b** (77%) as white crystals, mp 159–160 °C; ^{1}H NMR (CD_3OD): δ 7.47 (dd, 1H, J = 1.7, 8.1 Hz, aromatic C_3-*H*), 7.42 (d, 1H, J = 1.7 Hz, aromatic C_1-*H*), 7.28 (d, 1H, J = 7.9 Hz, aromatic C_4-*H*), 7.24 (dt, 1H, J = 1.5, 7.7 Hz, aromatic C_8-*H*), 7.12 (dd, 1H, J = 1.5, 7.7 Hz, aromatic C_6-*H*), 7.01 (dt, 1H, J = 1.5, 7.7 Hz, aromatic C_7-*H*), 6.96 (dd, 1H, J = 1.5, 7.7 Hz, aromatic C_9-*H*), 4.05 (m, 2H, CH_2-phenothiazine), 3.21 (m, 3H, piperidine $C_{2'}$-*H*, piperidine $C_{6'}$-H_2), 3.15 (s, 3H, CH_3-SO_2), 2.89 (s, 3H, CH_3-N(O)), 1.83–1.29 (m, 8H, CH_2-piperidine, piperidine $C_{3'}$-H_2, piperidine $C_{4'}$-H_2, piperidine $C_{5'}$-H_2); FAB MS: *m/z* (relative intensity %) 419 (MH^+, 32).

Anal.—Calcd for $C_{21}H_{26}N_2O_3S_2$: C, 60.13; H, 6.13; N, 6.68. Found: C, 60.28; H, 6.22; N, 6.69.

Trifluoperazine $N^{4'}$-Oxide (5b)[26]—This was prepared from **5a** by the same method as described for **1b** except that dichloromethane was used as solvent. The residue obtained after column chromatography was recrystallized from a mixture of ether and methanol (95:5) to give the $N^{4'}$-oxide **5b** (38%) as pale yellow, needle-shaped crystals, mp 108–109 °C; ^{1}H NMR ($CDCl_3$): δ 7.21–6.88 (m, 7H, aromatic H_7), 3.98 (t, 2H, J = 6.5 Hz, CH_2-phenothiazine), 3.16–3.13 (m, 7H, piperazine $C_{3'}$-H_2, piperazine $C_{5'}$-H_2, CH_3-N(O)), 2.60 (m, 6H, acyclic CH_2-$N^{1'}$, piperazine $C_{2'}$-H_2, piperazine $C_{6'}$-H_2), 1.93 (q, 2H, J = 6.6 Hz, $CH_2CH_2CH_2$); FAB MS: *m/z* (relative intensity %) 424 (MH^+, 53).

Anal.—Calcd for $C_{21}H_{24}F_3N_3OS$: C, 59.79; H, 5.71; N, 9.93. Found: C, 59.35; H, 5.65; N, 9.53.

Trifluoperazine $N^{1'}$,$N^{4'}$-Dioxide (5c)—This was prepared from **5a** by the same method as described for **1b** except that 2.5 equivalents (instead of 1.2 equivalents) of 3-chloroperoxybenzoic acid were utilized as oxidant and dichloromethane was used as solvent. The residue obtained subsequent to column chromatography was recrystallized from a mixture of ether and methanol (80:20) to give the $N^{1'}$,$N^{4'}$-dioxide **5c** (20%) as an amorphous white powder, mp 167–169 °C (dec); ^{1}H NMR (CD_3OD): δ 7.33 (d, 1H, J = 7.9 Hz, aromatic C_3-*H*), 7.27 (m, 3H, aromatic C_1-*H*, C_6-*H*, C_8-*H*), 7.19 (dd, 1H, J = 1.4, 6.9 Hz, aromatic C_9-*H*), 7.13 (d, 1H, J = 8.4 Hz, aromatic C_4-*H*), 7.03 (t, 1H, J = 7.7 Hz, C_7-*H*), 4.16 (m, 6H, CH_2-phenothiazine, acyclic CH_2-$N^{1'}$(O), piperazine $C_{2'}$-*He*, piperazine $C_{6'}$-*He*), 3.99 (m, 2H, piperazine $C_{2'}$-*Ha*, piperazine $C_{6'}$-*Ha*), 3.56 (m, 2H, piperazine $C_{3'}$-*He*, piperazine $C_{5'}$-*He*), 3.36 (s, 3H, CH_3-N(O)), 3.21 (m, 2H, piperazine $C_{3'}$-*Ha*, piperazine $C_{5'}$-*Ha*), 2.37 (m, 2H, $CH_2CH_2CH_2$); FAB MS: *m/z* (relative intensity %) 440 (MH^+, 15).

Anal.—Calcd for $C_{21}H_{24}F_3N_3O_2S$: C, 57.39; H, 5.50; N, 9.56. Found: C, 56.99; H, 5.61; N, 9.16.

Trifluoperazine $N^{1'}$,$N^{4'}$,*S*-Trioxide (5d)—This was prepared from **5a** by the same method as described for **1b** except that 4.0 equivalents (instead of 1.2 equivalents) of 3-chloroperoxybenzoic acid were utilized as oxidant and dichloromethane was used as solvent. The residue obtained subsequent to column chromatography was recrystallized from a mixture of ether and methanol (70:30) to give the $N^{1'}$,$N^{4'}$,*S*-trioxide **5d** (22%) as an amorphous white powder, mp 136–138 °C (dec); ^{1}H NMR (CD_3OD): δ 8.19 (d, 1H, J = 7.9 Hz, aromatic C_3-*H*), 8.07 (s, 1H, aromatic C_1-*H*), 8.02 (dd, 1H, J = 1.2, 8.0 Hz, aromatic C_6-*H*), 7.86 (m, 2H, aromatic C_8-*H*, C_9-*H*), 7.61 (d, 1H, J = 8.1 Hz, aromatic C_4-*H*), 7.42 (t, 1H, J = 8.0 Hz, aromatic C_7-*H*), 4.20 (m, 2H, CH_2-phenothiazine), 4.03 (m, 2H, acyclic CH_2-$N^{1'}$(O)), 3.62 (m, 2H, piperazine $C_{2'}$-*He*, piperazine $C_{6'}$-*He*), 3.53 (m, 2H, piperazine $C_{2'}$-*Ha*, piperazine $C_{6'}$-*Ha*), 3.44 (s, 3H, CH_3-N(O)), 3.41 (m, 2H, piperazine $C_{3'}$-*He*, piperazine $C_{5'}$-*He*), 3.06 (m, 2H, piperazine $C_{3'}$-*Ha*, piperazine $C_{5'}$-*Ha*), 2.47 (m, 2H, $CH_2CH_2CH_2$); FAB MS: *m/z* (relative intensity %) 456 (MH^+, 5). Insufficient material was available to obtain a sample that gave satisfactory elemental analyses data.

Chlorpromazine *N*′,*S*-Dioxide Maleate (1c)[27]—A solution of hydrogen peroxide (1.75 mL of a 60% w/v solution, 30.86 mmol) was added in a dropwise manner to a solution of **1a** (1.00 g, 3.13 mmol) in ethanol (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h and then treated with small portions of manganese dioxide powder until the absence of hydrogen peroxide was indicated with potassium iodide starch paper. The excess manganese dioxide was filtered, and the solvent from the filtrate was removed on a rotavapor. The residue was dissolved in dry methanol (20 mL) and treated with a solution of maleic acid (0.364 g, 3.14 mmol) in methanol at 4 °C for 8 h. The resultant solid was filtered and washed with methanol (cooled at −20 °C) to give the maleate salt **1c** (1.26 g, 86%) as cream-colored crystals, mp 146–147 °C; ^{1}H NMR (free base, $CDCl_3$): δ 7.89 (dd, 1H, J = 1.5, 7.7 Hz, aromatic C_4-*H*), 7.82 (d, 1H, J = 8.2 Hz, aromatic C_6-*H*), 7.66 (dt, 1H, J = 1.6 Hz, 7.1 Hz, aromatic C_8-*H*), 7.56 (d, 1H, J = 8.0 Hz, aromatic C_9-*H*), 7.52 (d, 1H, J = 1.8 Hz, aromatic C_1-*H*), 7.29 (t, 1H, J = 7.8 Hz, aromatic C_7-*H*), 7.23 (dd, 1H, J = 1.8, 7.8 Hz, aromatic C_3-*H*), 4.52 (m, 2H, CH_2-phenothiazine), 3.32 (t, 2H, J = 7.6 Hz, CH_2-N(O)), 3.03 and 2.99 (two s, 6H, $(CH_3)_2$N(O)), 2.53 (m, 2H, $CH_2CH_2CH_2$); FAB MS: *m/z* (relative intensity %) 351/353 (MH^+, 24/9).

Anal.—Calcd for $C_{21}H_{23}ClN_2O_6S$: C, 54.01; H, 4.96; N, 6.00. Found: C, 54.34; H, 4.90; N, 6.00.

Sulforidazine *N*′,*S*-Dioxide (4c)—This was prepared from **4a** by the same method as described for **1c**. The residue obtained after removal of solvents was recrystallized from methanol to give the *N*′,*S*-dioxide **4c** (20%) as white crystals, mp 178–181 °C; ^{1}H NMR (CD_3OD): δ 8.26 (d, 1H, J = 8.1 Hz, aromatic C_4-*H*), 8.14 (d, 1H, J =

1.4 Hz, aromatic C_1-*H*), 8.05 (dd, 1H, J = 0.8, 7.6 Hz, aromatic C_6-*H*), 7.95 (bd, 1H, J = 8.6 Hz, aromatic C_9-*H*), 7.85 (dt, 1H, J = 0.8, 7.5 Hz, aromatic C_8-*H*), 7.81 (dd, 1H, J = 1.3, 8.2 Hz, aromatic C_3-*H*), 7.43 (dt, 1H, J = 0.8, 7.5 Hz, aromatic C_7-*H*), 4.59 (m, 2H, CH_2-phenothiazine), 3.57 (m, 1H, piperidine $C_{2'}$-*H*), 3.26 (s, 3H, CH_3-SO_2), 3.16 (m, 2H, piperidine $C_{6'}$-H_2), 2.96 (s, 3H, CH_3-N(O)), 1.91–1.69 (m, 8H, CH_2-piperidine, piperidine $C_{3'}$-H_2, piperidine $C_{4'}$-H_2, piperidine $C_{5'}$-H_2); FAB MS: *m/z* (relative intensity %) 435 (MH^+, 75).

Anal.—Calcd for $C_{21}H_{26}N_2O_4S_2(H_2O)$: C, 55.73; H, 6.24; N, 6.19. Found: C, 55.88; H, 6.10; N, 6.27.

Results and Discussion

Phenothiazine antipsychotic agents invariably possess at least two readily oxidizable heteroatoms; one or more sulfur atoms and one or more aliphatic tertiary amine groups. Therefore, in initial work, various oxidizing agents were investigated as to their suitability in the synthesis of the *N*-oxide metabolite from the free base of the parent compound. Chlorpromazine (**1a**) was selected for this exploratory work because not only is it regarded as the prototype agent of this group of drugs but it has only two readily oxidizable heteroatoms. These heteroatoms are the sulfur atom at the 5-position of the phenothiazine ring and the nitrogen atom of the aliphatic tertiary amine group in the *N*-10 side chain. Reagents that have been utilized in the oxidation of chlorpromazine to chlorpromazine *N*-oxide (**1b**) include calcium hypochlorite[11] and hydrogen peroxide.[16] However, when investigated in the present work, analysis by thin-layer chromatography of the reaction mixtures indicated that both these reagents gave complex mixtures of products. For example, in the case of calcium hypochlorite, when the reported reaction conditions were employed, no *N*-oxide could be detected in the reaction mixture that contained primarily the 5-sulfoxide, 5-sulfone, and *N'*,*S*-dioxide analogues of chlorpromazine. This result is surprising in that use of this oxidizing agent is reported to give a 95% yield of chlorpromazine *N*-oxide from chlorpromazine.[11] Examination of other reagents (cumene hydroperoxide, monoperoxytetraphenylphthalic acid,[28] sodium metaperiodate, and tetrabutylammonium periodate) demonstrated that they preferentially oxidized the ring sulfur atom under the experimental conditions employed.

In the present work, the original published general procedure[29] of the synthesis of tertiary amine *N*-oxides with 3-chloroperoxybenzoic acid as an oxidizing agent was modified to obtain chlorpromazine *N*-oxide in high yield. The oxidation was performed at −70 °C in tetrahydrofuran rather than the commonly used chlorinated hydrocarbon solvents. The rationale for this modification in reaction conditions is that rapid reaction favors *S*-oxidation over *N*-oxidation, and solvents capable of hydrogen bonding with the peracid oxidant (e.g., alcohols and ethers) can effectively slow the reaction rate, thereby improving *N*-oxidation selectivity.[30]

The use of different oxidizing agents at low temperature demonstrated that with tetrahydrofuran as solvent preferential oxidation occurred at the aliphatic tertiary amine group in the *N*-10 side chain of chlorpromazine. The oxidizing agents tested included benzoyl peroxide, 3-chloroperoxybenzoic acid, and peroxydecanoic acid[28]; of these, 3-chloroperoxybenzoic acid was found to be the most selective. Moreover, the purification of this reagent is crucial in obtaining increased yields of the desired products. Although there have been previous reports of the use of this reagent in the synthesis of the *N*-oxide metabolites of phenothiazine antipsychotic agents, no details of the procedure or characterization of the final products have been reported.[31,32]

In the present report, the use of 1.2 equivalents of 3-chloroperoxybenzoic acid successfully yielded the *N*-oxides of fluphenazine, prochlorperazine, sulforidazine, and trifluoperazine (**2b–5b**, respectively). Thus, it was demonstrated that the aliphatic tertiary amine nitrogen underwent oxidation irrespective of whether it was acyclic as in chlorpromazine, cyclic as in the piperazine type phenothiazines fluphenazine, prochlorperazine, and trifluoperazine, or cyclic as in the piperidine-type phenothiazine sulforidazine. In the case of the piperazine ring oxidation occurred at the $N^{4'}$ nitrogen atom, which is the nitrogen atom most distant from the point of attachment to the phenothiazine ring system.

For those phenothiazine antipsychotic agents with more than one nitrogen atom in the *N*-10 side chain, the selectivity of the oxidizing agent can be further exploited. An increase in the molar amount of 3-chloroperoxybenzoic acid from 1.2 to 2.5 or 4.0 equivalents yielded, as the major product, the $N^{1'}$,$N^{4'}$-dioxide (**5c**) and $N^{1'}$,$N^{4'}$,*S*-trioxide (**5d**) of trifluoperazine, respectively. These observations indicate that under the reaction conditions employed the oxidizing agent was selective in the order piperazine $N^{4'}$, piperazine $N^{1'}$, and phenothiazine ring sulfur atoms. The chemical synthesis of neither **5c** nor **5d** has been reported previously, although the structurally related compound prochlorperazine $N^{1'}$,$N^{4'}$,*S*-trioxide was synthesized by treatment of prochlorperazine with hydrogen peroxide.[17] In the present work, this oxidizing reagent was suitable for the synthesis of the *N'*,*S*-dioxide compounds, specifically chlorpromazine *N'*,*S*-dioxide (**1c**) and sulforidazine *N'*,*S*-dioxide (**4c**).

The structural assignments of all compounds were substantiated by the presence of pseudomolecular ions in the chemical ionization MS (data not given) and FAB MS spectra and high-resolution ^{1}H NMR spectral data. With respect to the latter and in comparison with the spectrum of the parent drug, protons vicinal to the site of *N*-oxidation were greatly shifted downfield, whereas such was the case with all aromatic protons in ring *S*-oxidized products. Because in the case of fluphenazine the site of *N*-oxidation could not be unambiguously determined by high-resolution ^{1}H NMR spectra, spin decoupling experiments were conducted. For example, irradiation of the signal due to $CH_2CH_2CH_2$ at δ 1.92 resulted in the collapse of each of the two proton multiplets at δ 4.06 and δ 2.58. Therefore, these two latter signals were due to the protons of the two acyclic methylene groups vicinal to the central methylene group (i.e., CH_2-phenothiazine and CH_2-$N^{1'}$, respectively). The latter signal (δ 2.58, CH_2-$N^{1'}$) was at a similar position to that of the analogous protons of the parent drug. Consequently the site of *N*-oxidation was at the other piperazine $N^{4'}$ atom; namely, that most distant from the phenothiazine ring.

Conclusions

Of the various oxidants examined, the agent that showed the greatest selectivity for side chain *N*-oxidation as compared with phenothiazine ring *S*-oxidation of chlorpromazine was 3-chloroperoxybenzoic acid. A general procedure based on this oxidant enabled the synthesis of the *N*-oxides of five phenothiazine antipsychotic agents. Moreover, the selectivity of 3-chloroperoxybenzoic acid enabled the successful synthesis of the $N^{1'}$,$N^{4'}$-dioxide and $N^{1'}$,$N^{4'}$,*S*-trioxide analogues of trifluoperazine. The *N'*,*S*-dioxides of chlorpromazine and sulforidazine were obtained by oxidation of these drugs with hydrogen peroxide.

References and Notes

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