Synthesis of the Piperidinone Metabolites of Piperidine Type Phenothiazine Antipsychotic Drugs *via* Ruthenium Tetroxide Oxidation

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The lactam metabolites of the piperidine type phenothiazine antipsychotic drugs thioridazine, mesoridazine and sulforidazine were synthesized in six steps from commercially available 2-(2-hydroxyethyl)piperidine. The key step involved ruthenium tetroxide oxidation of *N*-protected 2-(2-chloroethyl)piperidine. The products were then oxidized to obtain the phenothiazine ring 5-sulfoxide analogues.

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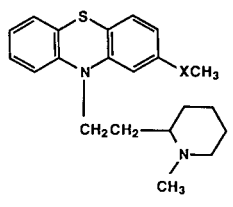
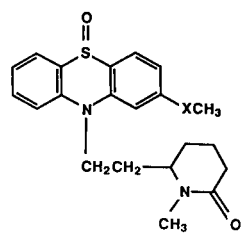
The piperidine type phenothiazine antipsychotic drugs include thioridazine (**1a**), mesoridazine (**1b**) and sulforidazine (**1c**) which only differ in the state of oxidation of the sulfur atom of the ring 2-substituent. The established routes of metabolism of these drugs in man and animals involve *S*-oxidation of the ring 2-substituent, *S*-oxidation and aromatic hydroxylation of the phenothiazine ring and *N*-demethylation of the piperidine ring *N*-substituent [1-3]. There is little known about the metabolism of the piperidine ring itself. The lactam derivatives **2a** and **2b** of mesoridazine ring sulfoxide and sulforidazine ring sulfoxide, respectively, have been tentatively identified on the basis of the electron impact mass spectra of the isolated metabolites as present in the extracts of urine of patients under chronic oral treatment with these drugs [3]. For other drugs with saturated nitrogen-containing heterocyclic ring systems including piperidine, it is well established in various species that the metabolites include the lactams and ring opened products [4-8].

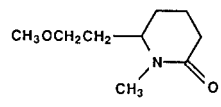
Samples of the lactam derivatives of piperidine type phenothiazine antipsychotic agents were required to enable their positive identification as metabolites in man and animals. These samples were also needed to develop qualitative and quantitative assays in order to investigate their importance in metabolic and pharmacokinetic studies. This report describes a facile synthetic route to the lactam derivatives of thioridazine, mesoridazine and sulforidazine **11a-c** and their respective ring sulfoxide compounds **12a-c**.





1a : X = S
1b : X = SO
1c : X = SO_2

2a : X = SO
2b : X = SO_2



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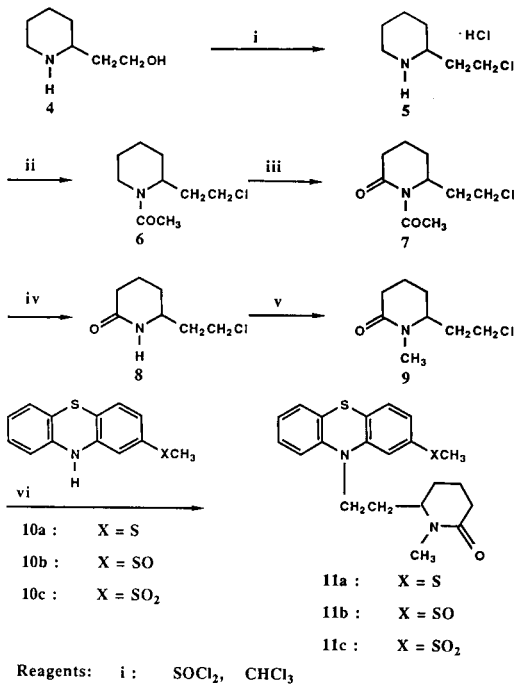
The approach planned to obtain **11a-c** was to react the synthon 6-(2-chloroethyl)-1-methyl-2-piperidinone (**9**) with the appropriate 2-substituted phenothiazine, **10a-c**. There are previous reports to **9** [9] or the suitable intermediate 6-(2-hydroxyethyl)-1-methyl-2-piperidinone [10,11]. These reported synthetic schemes involved in the key step either cyclization of an amino acid derivative [10] or reduction of a 2-pyridinone [11]. However, both these approaches required multiple steps from commercially available starting materials.

Ruthenium tetroxide oxidation of acylated cyclic amines to give lactams and/or imides [12] has recently found use in the conversion of 2-substituted piperidines to the analogous piperidinones [13,14]. Thus a synthetic approach to **9** was developed where in the key step the lactam functionality was introduced in the piperidine ring by oxidation using ruthenium tetroxide. The relatively cheap commercially available compound 2-(2-hydroxyethyl)piperidine (**4**) was used as starting material. The initial attempt to obtain the synthon **9** from **4** involved in turn acylation of both *N*H and *O*H groups, oxidation to provide the piperidinone derivative, *N*-deacylation, *N*-methylation and chlorination. Unfortunately in the case of the penultimate reaction the *N,O*-dimethylated compound **3** was obtained as the major product [15]. Hence the synthetic route to **9** was modified (Scheme 1) so that in the first step the alcohol **4** was converted to the chloro compound **5**. Subsequent reaction with acetic anhydride in pyridine produced the *N*-acetyl derivative **6**, which although stable at low temperature (0-4°) slowly decomposed at room temperature to the acyl ester of **4**. Treatment of **6** with a catalytic amount of ruthenium dioxide and an excess of sodium metaperiodate in a two-phase system of ethyl acetate-water [13], provided the piperidinone **7**. Subsequent deacylation and methylation gave the synthon **9**. Finally *N*-10 alkyla-

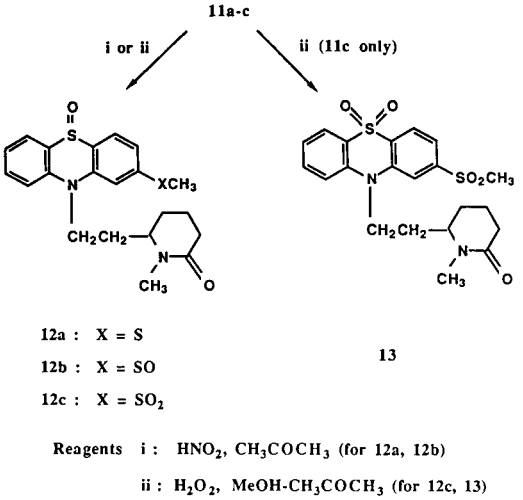
tion of the appropriate **10a-c** utilizing sodium hydride as base afforded racemic mixtures of the desired lactam compounds **11a-c**.

Scheme 1



The ring 5-sulfoxide analogues **12a-c** were obtained by use of a suitable oxidizing agent (Scheme 2). Nitrous acid is often favoured for such oxidations [16] but, whereas it was convenient for the synthesis of **12a** and **12b**, it did not react with **11c**. Therefore, hydrogen peroxide was used for such conversion where at room temperature **12c** was obtained while the sulfone **13** was obtained after reflux.

Scheme 2



The structural assignments of all compounds were substantiated by data from the ir, ^{1}H nmr and electron impact ms spectra. The electron impact ms of compounds tentatively identified in biological extracts as **12b** and **12c** were previously reported [3]. Although for both of these compounds some of the ions were common to both reported and present spectra, comparison is difficult especially due to the fact that the data were obtained from different laboratories on different instruments under different conditions. However, the availability of synthetic samples of these metabolites has now enabled unequivocal identification of the lactam metabolites of piperidine type phenothiazine antipsychotic agents in animals and man [15].

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Observed boiling points are also uncorrected. Tlc was carried out on aluminum sheets pre-coated (0.2 mm) with Kieselgel 60 F_{254} (E. Merck) and spots were examined either with an uv lamp (254 or 365 nm), or 0.5% ninhydrin in butan-1-ol spray followed by heat treatment. Flash column chromatography was performed with Merck silica gel 60 (40-63 μm). The ir spectra were obtained on a Beckman Acculab 4 spectrophotometer. The ^{1}H nmr spectra were recorded on a Bruker AM-300 spectrometer in deuteriochloroform solution. Chemical shifts are reported in delta units relative to tetramethylsilane. Mass spectra were obtained in the electron impact ionization mode (70 eV) on a VG Micromass 7070HE instrument coupled to a VG 2035 data system. Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer. Ruthenium (IV) oxide hydrate was obtained from Fluka Chemical Corp. Compounds **10a** and **10b** were gifts from Sandoz Inc., East Hanover, NJ and Sandoz Pharmaceuticals, Dorval, Quebec, Canada while **10c** was synthesized as previously reported [17]. All other chemicals were procured from Aldrich Chemical Co.

2-(2-Chloroethyl)piperidine Hydrochloride (**5**).

Thionyl chloride (20 ml, excess) was added dropwise to a stirred and cooled (0°) solution of 2-(2-hydroxyethyl)piperidine (**4**) (20.0 g, 0.155 mole) in anhydrous chloroform (150 ml). After warming gradually to room temperature, the reaction mixture was heated under reflux for 2 hours. The solvent and excess thionyl chloride were removed under reduced pressure. The brown solid residue was washed with acetone and then dissolved in methanol. Addition of acetone gave white needles which were filtered and recrystallized from acetone-methanol to yield the salt **5** (27.0 g, 93%) as colorless needles, mp 158-159° (ref [18] mp 160-162°); ir (potassium bromide): ν 3480 (N-H) cm^{-1}; ^{1}H nmr: δ 9.58 (2H, br, N^+H_2 deuterium oxide-exchangeable), 3.87 (1H, m, CHCl), 3.70 (1H, m, CHCl), 3.49 (1H, m, C_6-H), 3.26 (1H, br, C_2-H), 2.98 (1H, m, C_6-H), 2.55 (1H, m, C*H*CH_2Cl), 2.22 (1H, m, C*H*CH_2Cl), 2.06 (5H, m, C_3-H_2, C_4-H, C_5-H_2), 1.54 (1H, m, C_4-H); ms: m/z (relative intensity %) 149/147 ($M^{+\cdot}$, 0.9/2.2), 84 (100).

Anal. Calcd. for $C_7H_{15}Cl_2N$: C, 45.90; H, 8.20; N, 7.65. Found: C, 45.73; H, 8.51; N, 7.38.

1-Acetyl-2-(2-chloroethyl)piperidine (**6**).

To a solution of **5** (10.0 g, 54.8 mmoles) in pyridine (80 ml) was added acetic anhydride (60 ml). The solution was stirred at room temperature for 1 hour and then poured into water and extracted with ethyl acetate. The combined organic extracts were washed with 1*N* hydrochloric acid and then water. The solution was dried (sodium sulfate) and evaporated under reduced pressure. The resultant yellow oil was distilled *in vacuo* to obtain **6** (9.7 g, 93%) as a colourless liquid, bp 127° (1.5 mm Hg); ir (neat): ν 1650 (C=O) cm^{-1}; ^1H nmr: δ 4.92 (1H, m, C_6-H), 4.54 (1H, m, C_2-H), 4.20 (1H, m, C_6-H), 3.52 (2H, m, CH_2Cl), 3.15 (1H, m, C*H*CH_2Cl), 2.53 (1H, m, C*H*CH_2Cl), 2.17 (3H, s, CH_3), 1.75-1.60 (6H, m, C_3-H_2, C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 191/189 ($M^{+\cdot}$, 3.4/7.0), 154 (19), 126 (45), 84 (100).

Anal. Calcd. for $C_9H_{16}ClNO$: C, 57.14; H, 8.47; N, 7.41. Found: C, 57.38; H, 8.78; N, 7.31.

1-Acetyl-6-(2-chloroethyl)-2-piperidinone (**7**).

A solution of **6** (10.0 g, 52.9 mmoles) in ethyl acetate (160 ml) was added dropwise to a stirred mixture of a catalytic amount of ruthenium(IV) oxide hydrate (350 mg) in aqueous 10% sodium metaperiodate (500 ml). After the addition was completed, the stirring was continued at room temperature for 4 hours. The two layers were separated and the aqueous solution was extracted with ethyl acetate. The combined organic extracts were treated with isopropyl alcohol (20 ml) for 2 hours to destroy excess ruthenium oxidant. The black precipitate was filtered, and the filtrate was washed with water, dried (sodium sulfate) and evaporated *in vacuo*. Distillation of the residual oil afforded **7** (8.4 g, 78%) as a colorless oil, bp 125-126° (1.0 mm Hg); ir (neat): ν 1700 (d, C=O) cm^{-1}; ^1H nmr: δ 4.72 (1H, m, C_6-H), 3.57 (2H, m, CH_2Cl), 2.60 (2H, m, C_3-H_2), 2.44 (3H, s, CH_3), 2.15-1.62 (6H, m, C_4-H_2, C_5-H_2, C$H_2$$CH_2Cl$); ms: m/z (relative intensity %) 205/203 ($M^{+\cdot}$, 0.4/1.0), 168 (22), 163/161 (7/20), 140 (13), 126 (13), 112 (15), 99 (100), 71 (11).

Anal. Calcd. for $C_9H_{14}ClNO_2$: C, 53.20; H, 6.90; N, 6.90. Found: C, 52.90; H, 7.06; N, 6.83.

6-(2-Chloroethyl)-2-piperidinone (**8**).

A mixture of **7** (3.5 g, 17.2 mmoles) and 70.0 g of basic aluminum oxide in 400 ml of *n*-hexane-ethyl acetate (1:2) was stirred at room temperature overnight. The reaction mixture was filtered and the residual aluminum oxide was washed with dichloromethane. The combined filtrates were evaporated under reduced pressure. Crystallization from ether with a few drops of dichloromethane gave **8** (1.8 g, 66%) as colorless needles, mp 125.5-126°; ir (potassium bromide): ν 3220 (N-H), 1655 (C=O) cm^{-1}; ^1H nmr: δ 6.76 (1H, br, NH), 3.68 (2H, m, CH_2Cl), 3.49 (1H, m, C_6-H), 2.35 (2H, m, C_3-H_2), 2.05-1.68 (4H, m, C_5-H_2, C$H_2$$CH_2Cl$), 1.45 (1H, m, C_4-H), 1.22 (1H, m, C_4-H); ms: m/z (relative intensity %) 163/161 ($M^{+\cdot}$, 33/100), 128 (10), 105 (8).

Anal. Calcd. for $C_7H_{12}ClNO$: C, 52.17; H, 7.45; N, 8.70. Found: C, 52.23; H, 7.58; N, 8.43.

6-(2-Chloroethyl)-1-methyl-2-piperidinone (**9**).

To a mixture of **8** (1.2 g, 7.5 mmoles) and methyl iodide (5 ml, excess) in dimethylformamide (60 ml) was added sodium hydride (0.5 g, 80% dispersion in mineral oil, freshly washed with toluene). The reaction mixture was stirred at room temperature overnight, and then filtered, poured into water and extracted with ether. The combined extracts were dried (sodium sulfate), decolorized by charcoal and evaporated *in vacuo*. The residual oil was distilled to produce synthon **9** (1.1 g, 87%) as a colorless liquid, bp 127° (1.4 mm Hg); ir (neat): ν 1640 (C=O) cm^{-1}; ^1H nmr: δ 3.59 (3H, m, C_6-H, CH_2Cl), 2.95 (3H, s, CH_3), 2.36 (2H, m, C_3-H_2), 2.18 (1H, m, C*H*CH_2Cl), 2.04-1.74 (5H, m, C_4-H_2, C_5-H_2, C*H*CH_2Cl); ms: m/z (relative intensity %) 177/175 ($M^{+\cdot}$, 1.8/4.4), 112 (100), 84 (16).

Anal. Calcd. for $C_8H_{14}ClNO$: C, 54.86; H, 8.00; N, 8.00. Found: C, 55.04; H, 7.75; N, 7.75.

General Procedure for the Reaction of 2-(2-(Chloroethyl)piperidine **9** with 2-Substituted Phenothiazines **10a-c**.

To a solution of the appropriate phenothiazine **10** (2.0 mmoles) and the chloro compound **9** (0.39 g, 2.2 mmoles) in dry toluene (10 ml) was added a suspension of sodium hydride (0.36 g, 80% dispersion in mineral oil, freshly washed with toluene) in dry toluene (10 ml). The resultant mixture was heated under reflux for 22 hours under nitrogen in the absence of direct intense light. After cooling, the mixture was poured into water (200 ml) containing ammonium chloride (2.0 g) and extracted with toluene. The combined extracts were successively washed with 1*N* hydrochloric acid and water and then dried. Evaporation of toluene under vacuum provided a crude product which was purified by silica gel flash chromatography using 3% methanol in toluene as eluent to give **11**.

10-[2-(1-Methylpiperidin-2-on-6-yl)ethyl]-2-methylthio-10*H*-phenothiazine (**11a**).

This compound was obtained (78%) as a thick yellow oil; ir (dichloromethane): ν 1645 (C=O) cm^{-1}; ^1H nmr: δ 7.20-6.79 (7H, m, aromatic H_7), 3.96 (1H, m, phenothiazinyl CH), 3.86 (1H, m, phenothiazinyl CH), 3.49 (1H, m, piperidinone C_6-H), 2.71 (3H, s, NCH_3), 2.47 (3H, s, SCH_3), 2.30 (4H, m, piperidinonyl CH_2, piperidinone C_3-H_2), 1.94-1.72 (4H, m, piperidinone C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 384 ($M^{+\cdot}$, 31), 258 (9), 244 (20), 139 (70), 112 (34), 96 (20), 83 (100).

Anal. Calcd. for $C_{21}H_{24}N_2OS_2$: C, 65.63; H, 6.25; N, 7.29. Found: C, 65.85; H, 6.46; N, 7.43.

10-[2-(1-Methylpiperidin-2-on-6-yl)ethyl]-2-methylsulfinyl-10*H*-phenothiazine (**11b**).

This compound was obtained (77%) as a thick yellow oil; ir (dichloromethane): ν 1645 (C=O), 1060 (S=O) cm^{-1}; ^1H nmr: δ 7.30-6.92 (7H, m, aromatic H_7), 4.03 (1H, m, phenothiazinyl CH), 3.93 (1H, m, phenothiazinyl CH), 3.49 (1H, m, piperidinone C_6-H), 2.73 (3H, s, NCH_3), 2.70 (3H, s, $SOCH_3$), 2.30 (4H, m, piperidinonyl CH_2, piperidinone C_3-H_2), 1.92-1.74 (4H, m, piperidinone C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 400 ($M^{+\cdot}$, 100), 386 (19), 385 (44), 384 (44), 260 (25), 259 (19), 258 (22), 246 (16), 245 (27), 244 (33), 140 (20), 112 (94).

Anal. Calcd. for $C_{21}H_{24}N_2O_2S_2$: C, 63.00; H, 6.00; N, 7.00. Found: C, 62.86; H, 6.28; N, 6.86.

10-[2-(1-Methylpiperidin-2-on-6-yl)ethyl]-2-methylsulfonyl-10*H*-phenothiazine (**11c**).

This compound was obtained (72%) as a thick yellow oil; ir (dichloromethane): ν 1645 (C=O), 1325 (SO_2), 1160 (SO_2) cm^{-1}; ^1H nmr: δ 7.35-6.92 (7H, m, aromatic H_7), 3.99 (1H, m, phenothiazinyl CH), 3.91 (1H, m, phenothiazinyl CH), 3.49 (1H, m, piperi-

dinone C_6-H), 3.04 (3H, s, SO_2CH_3), 2.75 (3H, s, NCH_3), 2.30 (4H, m, piperidinonyl CH_2, piperidinone C_3-H_2), 1.91-1.71 (4H, m, piperidinone C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 416 ($M^{+\cdot}$, 85), 291 (10), 290 (25), 277 (26), 276 (19), 211 (11), 198 (12), 197 (16), 196 (10), 140 (27), 139 (11), 113 (13), 112 (100), 98 (14).

Anal. Calcd. for $C_{21}H_{24}N_2O_3S_2$: C, 60.58; H, 5.77; N, 6.73. Found: C, 60.87; H, 5.69; N, 6.79.

General Procedure for the Oxidation of Phenothiazines **11a-b** with Nitrous Acid.

A solution of 10% aqueous nitrous acid (30 ml) was added dropwise to a stirred solution of phenothiazine **11a** or **11b** (0.78 mmole) in acetone (30 ml). The reaction mixture was stirred at room temperature for a further 3 hours. After neutralization with aqueous ammonia, the mixture was extracted with dichloromethane. The combined extracts were dried (sodium sulfate) and the solvent was removed on a rotavapor. Crystallization from hexane with a few drops of dichloromethane gave **12a** and **12b** in 90 and 82% yield, respectively.

10-[2-(1-Methylpiperidin-2-on-6-yl)ethyl]-2-methylthio-10*H*-phenothiazine-5-sulfoxide (**12a**).

This compound was obtained as red crystals, mp 99-100°; ir (potassium bromide): ν 1643 (C=O), 1040 (S=O) cm^{-1}; ^1H nmr: δ 7.94-7.08 (7H, m, aromatic H_7), 4.26 (2H, m, phenothiazinyl CH_2), 3.51 (1H, m, piperidinone C_6-H), 2.85 (3H, s, NCH_3), 2.57 (3H, s, SCH_3), 2.38 (4H, m, piperidinonyl CH_2, piperidinone C_3-H_2), 2.06-1.77 (4H, m, piperidinone C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 400 ($M^{+\cdot}$, 32), 385 (14), 384 (39), 382 (20), 259 (27), 258 (100), 245 (21), 244 (39), 226 (21), 211 (13), 185 (16), 180 (10), 138 (24), 112 (54), 84 (12).

Anal. Calcd. for $C_{21}H_{24}N_2O_2S_2$: C, 63.00; H, 6.00; N, 7.00. Found: C, 62.72; H, 5.78; N, 6.80.

10-[2-(1-Methylpiperidin-2-on-6-yl)ethyl]-2-methylsulfinyl-10*H*-phenothiazine-5-sulfoxide (**12b**).

This compound was obtained as a red solid, mp 90-92°; ir (potassium bromide): ν 1645 (C=O), 1065 (S=O), 1043 (S=O) cm^{-1}; ^1H nmr: δ 8.08-7.21 (7H, m, aromatic H_7), 4.37 (2H, m, phenothiazinyl CH_2), 3.65 (1H, m, piperidinone C_6-H), 2.86 (3H, s, NCH_3), 2.81 (3H, s, $SOCH_3$), 2.41 (4H, m, piperidinonyl CH_2, piperidinone C_3-H_2), 2.09-1.80 (4H, m, piperidinone C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 416 ($M^{+\cdot}$, 20), 401 (14), 400 (37), 399 (11), 398 (11), 385 (13), 384 (15), 276 (19), 275 (27), 274 (100), 261 (13), 260 (19), 259 (33), 258 (29), 246 (12), 245 (21), 244 (21), 228 (11), 212 (10), 211 (11), 197 (12), 138 (21), 112 (64), 84 (14).

Anal. Calcd. for $C_{21}H_{24}N_2O_3S_2$: H, 5.77; N, 6.73. Found: H, 5.61; N, 7.11.

10-[2-(1-Methylpiperidin-2-on-6-yl)ethyl]-2-methylsulfonyl-10*H*-phenothiazine-5-sulfoxide (**12c**).

Compound **11c** (139 mg, 0.33 mmole) was dissolved in a mixture of methanol and acetone (6:1, 35 ml). Hydrogen peroxide (30%, 5 ml) was added to the mixture dropwise. The reaction solution was stirred at ambient temperature for 36 hours and then poured into water and extracted with dichloromethane. The combined organic extracts were dried (sodium sulfate) and evaporated. The residue was crystallized from hexane with a few drops of dichloromethane to give **12c** as yellowish crystals (116 mg, 82%), mp 207-208°; ir (potassium bromide): ν 1640 (C=O), 1325 (SO_2), 1165 (SO_2), 1040 (S=O) cm^{-1}; ^1H nmr: δ 8.15-7.35 (7H, m, aromatic H_7), 4.36 (2H, m, phenothiazinyl CH_2), 3.49 (1H, m, piperidinone C_6-H), 3.11 (3H, s, SO_2CH_3), 2.87 (3H, s, NCH_3), 2.40 (4H, m, piperidinonyl CH_2, piperidinone C_3-H_2), 2.16-1.82 (4H, m, piperidinone C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 432 ($M^{+\cdot}$, 10), 417 (18), 416 (66), 292 (13), 291 (25), 290 (100), 277 (44), 276 (21), 258 (12), 211 (16), 198 (26), 197 (22), 196 (13), 179 (10), 140 (22), 139 (11), 138 (11), 113 (12), 112 (98), 98 (58).

Anal. Calcd. for $C_{21}H_{24}N_2O_4S_2$: C, 58.33; H, 5.56; N, 6.48. Found: C, 57.84; H, 5.46; N, 6.25.

10-[2-(1-Methylpiperidin-2-on-6-yl)ethyl]-2-methylsulfonyl-10*H*-phenothiazine-5-sulfone (**13**).

This was prepared from compound **11c** by the method described for **12c** except that the reaction mixture was heated under reflux for 10 hours. The ring-sulfone **13** was obtained (80%) as an orange powder, mp 259-260°; ir (potassium bromide): ν 1640 (C=O), 1320 (br, SO_2), 1165 (br, SO_2) cm^{-1}; ^1H nmr: δ 8.39-7.48 (7H, m, aromatic H_7), 4.28 (2H, m, phenothiazinyl CH_2), 3.49 (1H, m, piperidinone C_6-H), 3.12 (3H, s, SO_2CH_3), 2.80 (3H, s, NCH_3), 2.48 (4H, m, piperidinonyl CH_2, piperidinone C_3-H_2), 1.95-1.75 (4H, m, piperidinone C_4-H_2, C_5-H_2); ms: m/z (relative intensity %) 448 ($M^{+\cdot}$, 0.5), 416 (13), 401 (18), 400 (53), 385 (22), 384 (34), 277 (17), 276 (12), 275 (14), 274 (73), 261 (12), 260 (19), 259 (27), 258 (33), 246 (13), 245 (25), 244 (29), 226 (10), 211 (12), 198 (22), 197 (15), 185 (11), 179 (10), 140 (15), 138 (15), 113 (13), 112 (100), 100 (10), 98 (39).

Anal. Calcd. for $C_{21}H_{24}N_2O_5S_2$: C, 56.25; H, 5.36; N, 6.25. Found:C, 55.97; H, 5.80; N, 6.34.

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