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The thioridazine metabolites 7-hydroxythioridazine (**2a**) and 7-hydroxysulforidazine (**2b**) were synthesized. Commercial 4-chloro-3-nitrophenylmethylsulfone was converted to the corresponding 4-thiol through an intermediate xanthate ester. Subsequent zinc metal reduction provided the 3-amino thiolate. This salt was condensed with chloroquinone to yield 7-hydroxy-2-methylsulfonylphenothiazine which was then protected as the isopropyl ether. *N*-Alkylation with 2-(2-chloroethyl)-1-methylpiperidine using sodium hydroxide, then ether cleavage, afforded **2b**. The *N*-alkylation followed by reduction with diisobutylaluminum hydride and deblocking yielded **2a**. These reference standards will assist in an exploration of the potential role of metabolically formed **2a** and **2b** in the neuroleptic response to thioridazine.

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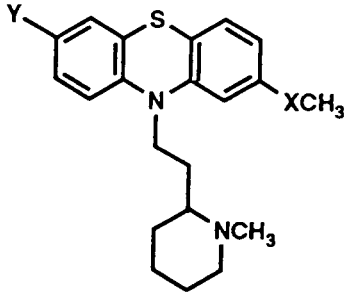
The phenothiazine neuroleptic *rac*-thioridazine (**1a**) undergoes extensive metabolism in man [2] and rat [3], with less than 1% of an oral dose excreted unchanged. The biotransformation products of **1a** favor a biliary over an urinary route of elimination and exhibit minimal enterohepatic recirculation. Approximately 20% of the **1a** elimination products have been structurally identified. These include side-chain and ring *S*-oxides and/or *N*-desmethyl species [3,4]. Of these, at least three exhibit pronounced pharmacological activity [5,6]. The side-chain sulfone (sulforidazine, **1b**) and side-chain sulfoxide (mesoridazine, **1c**) metabolites frequently approach or exceed, respectively, the circulating concentrations of the parent drug [7] and are marketed neuroleptics in their own right. Further, blood concentrations of the ring sulfoxide metabolite have been correlated with the incidence of cardiac toxicity [8].



1a : X = S, Y = H
1b : X = SO_2, Y = H
1c : X = SO, Y = H
2a : X = S, Y = OH
2b : X = SO_2, Y = OH

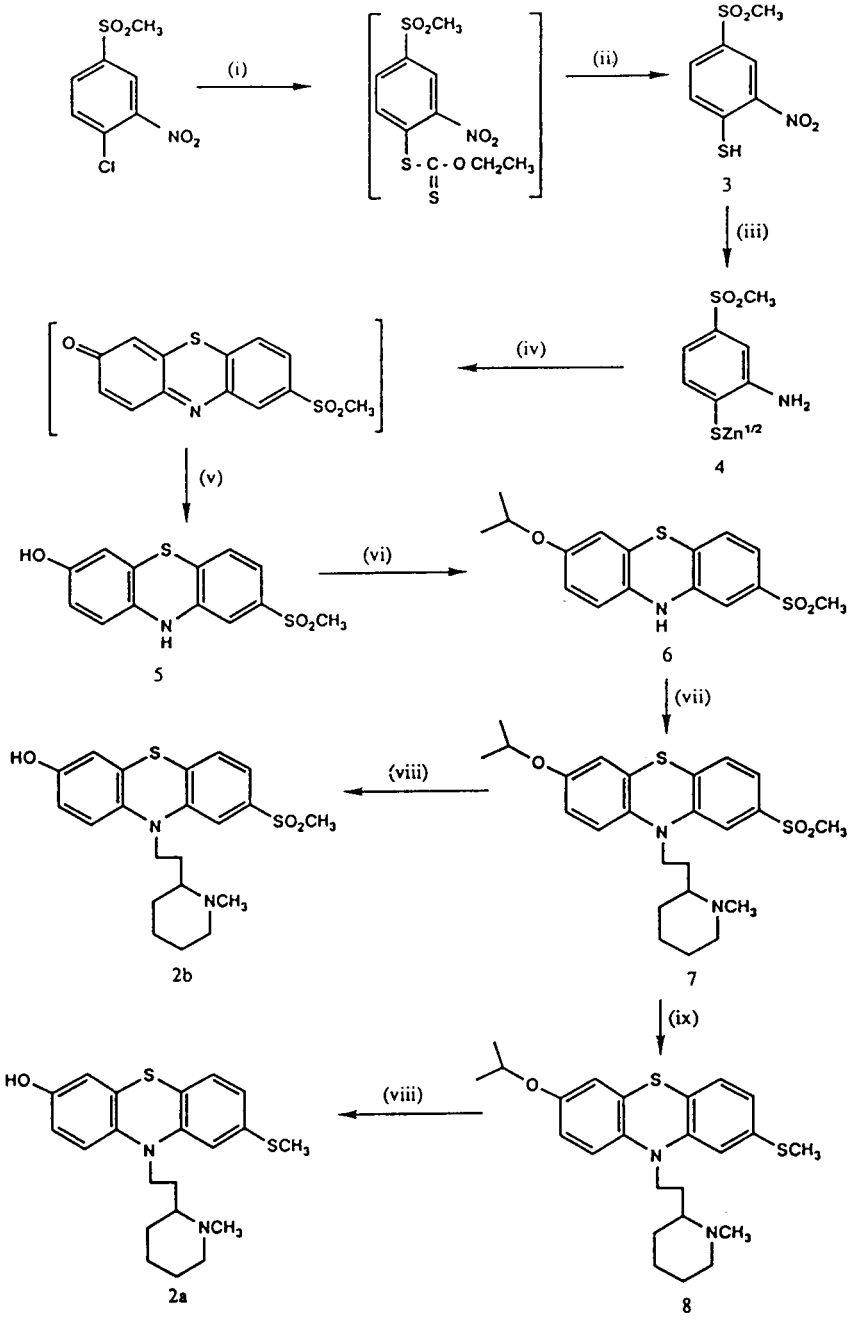
Figure 1

The metabolic fate of the remaining 80% of a dose of **1a** has been the subject of conjecture. Indirect evidence from rat studies indicate that the preponderance of the **1a** elimination products are glucuronides of hydroxylated derivatives [3]. Hydroxylated metabolites of **1a** and **1c** have been reported to be routinely detected in patient urine using various chromatographic methods [9]. Papadopoulos *et al.* [10] reported that after administration of **1a** or **1c**, human fecal samples contained primarily 7-hydroxy-**1a** (**2a**) and *nor*-**2a**, with lesser amounts of 7-hydroxy-**1b** (**2b**) and corresponding conjugates. After dosing with **1b**, urine and feces contained mainly **2b**. Ganes and Midha [11] have similarly detected hydroxylated metabolites in dog plasma after oral administration of **1b**.

The present work describes the first synthesis of reference standards of **2a** and **2b**. These purported metabolites of **1a** and **1b** will assist in the unequivocal structure elucidation of the phenolic elimination products. Further, the availability of **2a** and **2b** will permit an assessment of the effects on dopamine receptor function; pertinent to antipsychotic response. Such studies may reveal a clinically significant role associated with the metabolic formation of **2a** and **2b**, as finds precedents with the active 7-hydroxylated metabolites of the phenothiazine drugs chlorpromazine [12,13] and fluphenazine [14,15]. The pharmacological evaluation of **2a** and **2b** is currently in progress.

The synthetic route used to prepare **2a** and **2b** is depicted in Scheme I. An initial attempt to prepare the key intermediate, 4-methylsulfonyl-2-nitrobenzenethiol (**3**), through a disulfide derived from commercial 4-chloro-3-nitrophenylmethylsulfone was unsuccessful [16]. However, thiol **3** was produced in good yield from the above starting material using potassium xanthate followed by *in situ* alkaline hydrolysis. Dissolving metal reduction of **3** by a modification of the method of Nodiff and Hausman [17] provided the desired zinc salt **4**. Condensation of this thiolate with chlorohydroquinone in the presence of oxygen, followed by hydrosulfite reduction [17], afforded 7-hydroxy-2-methylsulfonylphenothiazine (**5**). The phenolic group was then protected as the isopropyl ether **6** by treatment with 2-iodopropane in dimethylformamide in the

Scheme I



Reagents:(i) $CH_3CH_2OC(=S)SK$, EtOH; (ii) KOH/H_2O; (iii)1. Zn dust/AcOH, HCl, 2. $ZnCl_2$/NaOH; (iv) Chlorohydroquinone, O_2; (v) $Na_2S_2O_4$; (vi) $(CH_3)_2CHI$, K_2CO_3 - DMF; (vii) 2 (2-chloroethyl)-1-methylpiperidine, NaOH; (viii) BCl_3; (ix) DIBAL.

presence of potassium carbonate [18]. Subsequent *N*-alkylation with 2(2-chloroethyl)-1-methylpiperidine [19] using sodium hydroxide in toluene [20] provided **7**. Deblocking with boron trichloride [18] yielded the target compound **2b**. While lithium aluminum hydride was ineffective in reducing sulfone **7**, diisobutylaluminium hydride (D1BAL) in toluene [21] effected this transformation, producing sulfide **8**. Finally, deblocking of **8** yielded **2a**.

EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Water of hydration was confirmed by the presence of a broad peak centered at approximately 3.4 ppm in the ^{1}H nmr spectrum which was transformed into a sharp singlet (DOH) by the addition of deuterium oxide. The tlc was on silica gel media (Kodak 13181). Column chromatographic separations were performed on Kieselgel 60 (70-230 mesh) obtained from E. Merck and Co. High resolution ^{1}H nmr spectra were acquired on a Varian VXR-400. Chemical shifts are presented in parts per million downfield from tetramethylsilane as the internal standard, and the relative peak areas given to the nearest whole number. Electron impact mass spectra (ms) were obtained on a Finnigan 4000 with Teknivent data system (St. Louis, MO), acquiring masses greater than m/z 50. Samples (ms) for compounds **6**, **7**, and **8** were gas chromatographed (gc) with helium (50 cm/sec) on a 30 m x 0.32 mm, 0.25 μm film thickness dimethylsilicone fused-silica column (DB-1, J & W Scientific, Folsom, CA) operated at 250°. The ms data are for an electron energy of 70 eV and reported as m/z (intensity relative to base peak). The 4-chloro-3-nitrophenylmethylsulfone was obtained commercially from Parish Chemical Co. (Orem, Utah) and potassium ethylxanthate was Pfaltz and Bauer, Inc. (Waterbury, CT).

4-Methylsulfonyl-2-nitrobenzenethiol (**3**).

A suspension of 4-chloro-3-nitrophenylmethylsulfone (8.23 g, 34.92 mmoles) in ethanol (165 ml) was warmed at 50° to give a solution, then cooled to ambient temperature. To this lightly precipitated solution was added potassium ethylxanthate (11.2 g, 69.86 mmoles) and the reaction mixture was stirred at room temperature for 18 hours. A solution of potassium hydroxide (3.92 g, 69.88 mmoles) in water (20 ml) was then added to the reaction mixture and the dark yellow solution was stirred for 44 hours. The reaction mixture was evaporated to near dryness under reduced pressure and diluted with cold water (200 ml). The *p*H of the resulting suspension was reduced from 10.2 to 3.5 by the slow addition of 2 *N* hydrochloric acid with stirring and cooling in ice bath. The light yellow suspension produced was cooled in an ice bath for another hour and the product was collected by filtration and dried under vacuum at 60° for 18 hours to afford 7.2 g (88%) of **3**. An analytical sample was obtained by washing with toluene and recrystallization from toluene-methanol, mp 195-197°; ^{1}H nmr (DMSO-d_6): δ 3.38 (s, 3H, CH_3), 7.77 (d, 1H, 6-H, J_o = 8.56 Hz), 8.17 (dd, 1H, 5-H, J_o = 8.36 Hz, J_m = 2.04 Hz), 8.69 (d, 1H, 3-H, J_m = 1.96 Hz); ms: m/z 233 (M^+, 1).

Anal. Calcd. for $C_7H_7NO_4S_2$: C, 36.04; H, 3.02; N, 6.00. Found: C, 36.40; H, 2.79; N, 6.24.

2-Amino-4-methylsulfonylbenzenethiol Zinc Salt (**4**).

A mixture of 6.6 g (28.29 mmoles) of **3**, 283 ml of glacial acetic acid and 11 ml of concentrated hydrochloric acid was heated to 60°. External heating was then discontinued and zinc dust (21.76 g, 0.33 g-atom) was added in portions to maintain the reaction temperature at 60-65°. During zinc addition, the reaction mixture turned from yellow to yellow-green and finally to zinc color. After the addition, the reaction was kept at 60° for 1 hour and at reflux temperature for another hour whereupon the mixture was cooled to room temperature and filtered to remove excess zinc. The yellow filtrate was evaporated to dryness under reduced pressure and the white residue was treated with a solution of 1.22 g (30.5 mmoles) of sodium hydroxide in 250 ml water. The suspension was warmed to improve solubility, then added to a solution of 2.1 g (15.4 mmoles) of zinc chloride in 6.3 ml acetic acid and 35 ml water, followed by heating at reflux for 20 minutes. The suspension was filtered hot and the white residue was dried under vacuum at 60° for 18 hours to afford 4.35 g (66%) of salt **4**. An analytical sample was obtained by recrystallization from methanol-dimethylformamide, mp >260° darkens; ^{1}H nmr (DMSO-d_6): δ 3.06 (s, 3H, CH_3), 5.75 (s, 2H, NH_2), 7.00 (dd, 1H, 5-H, J_o = 8.28 Hz, J_m = 1.96 Hz), 7.24 (d, 1H, 3-H, J_m = 1.96 Hz), 7.46 (d, 1H, 6-H, J_o = 8.08 Hz); ms: m/z 469 (M, 1$^+$).

Anal. Calcd. for $C_{14}H_{16}N_2O_4S_4Zn \cdot 0.75H_2O$: C, 34.80; H, 3.65; N, 5.79. Found: C, 34.44; H, 3.32; N, 5.79.

7-Hydroxy-2-methylsulfonylphenothiazine (**5**).

A solution of 1.26 g (31.5 mmoles) of sodium hydroxide in 10.15 ml of water was added to a mixture of 4.16 g (8.87 mmoles) of pulverized **4**, 4.50 g (31.25 mmoles) of chlorohydroquinone and 100 ml of ethanol. The reaction was heated at reflux and a rapid stream of oxygen was introduced below its surface for 4 hours. Filtration of the hot mixture provided a brown solid and dark brown filtrate. The filtrate was poured into 360 ml of cold water containing 5.4 g (31 mmoles) of sodium hydrosulfite. The resulting light tan suspension was first extracted with ether (3 x 50 ml) and then with ethyl acetate (3 x 100 ml). The combined organic extracts were dried over magnesium sulfate and sodium sulfate and evaporated to dryness under reduced pressure to afford a dark brown residue. This material was coated on 1 g of silica gel and applied to a silica gel column (2.5 x 32 cm) prepacked in toluene. After flushing the column with toluene to remove unreacted chlorohydroquinone, the product was eluted with 2% methanol in toluene. Appropriate fractions were pooled and evaporated to dryness and the residue recrystallized from toluene-methanol to afford 2.49 g (48%) of **5**, mp 199-201° (with preliminary softening); ^{1}H nmr (DMSO-d_6): δ 3.13 (s, 3H, CH_3), 6.38 (d, 1H, 6-H, J_m = 2.60 Hz), 6.46 (dd, 1H, 8-H, J_o = 8.52 Hz, J_m = 2.56 Hz), 6.52 (d, 1H, 9-H, J_o = 8.52 Hz), 7.08 (d, 1H, 1-H, J_m = 1.92 Hz), 7.12 (d, 1H, 4-H, J_o = 7.96 Hz), 7.17 (dd, 1H, 3-H, J_o = 8.08 Hz, J_m = 1.88 Hz), 8.66 (1H, NH); ms: m/z 293 (M^+, 91).

Anal. Calcd. for $C_{13}H_{11}NO_3S_2$: C, 53.23; H, 3.78; N, 4.77. Found: C, 53.56; H, 3.71; N, 4.76.

7-Isopropoxy-2-methylsulfonylphenothiazine (**6**).

Phenothiazine **5** (1.9 g, 6.48 mmoles), potassium carbonate (1.68 g, 12.15 mmoles), and 2-iodopropane (3.63 g, 21.35 mmoles) were stirred in dry dimethylformamide (30 ml) under nitrogen for 20 hours. The reaction mixture was filtered, the residue washed with methanol (10 ml) and the combined filtrate evaporated to dryness under reduced pressure. The dark yellow residue was recrystallized from toluene-methanol to afford 1.51 g (70%) of **6**, mp 184-186° (with preliminary softening); ^{1}H nmr (DMSO-d_6): δ 1.19 [s, 3H, $(CH_3)_2CH$], 1.20 [s, 3H, $(CH_3)_2CH$], 3.14 (s, 3H, SO_2CH_3), 4.44 [sept, 1H, $(CH_3)_2CH$], 6.57 (d, 1H, 6-H, J_m = 2.56 Hz), 6.58 (d, 1H, 9-H, J_o = 8.76 Hz), 6.62 (dd, 1H, 8-H, J_o = 8.58 Hz, J_m = 2.53 Hz), 7.09 (d, 1H, 1-H, J_m = 1.92 Hz), 7.13 (d, 1H, 4-H, J_o = 7.95 Hz), 7.19 (dd, 1H, 3-H, J_o = 8.04 Hz, J_m = 1.92 Hz), 8.76 (1H, NH); gc-ms: m/z 335 (M^+, 31).

Anal. Calcd. for $C_{16}H_{17}NO_3S_2$: C, 57.29; H, 5.11; N, 4.18. Found: C, 57.63; H, 5.12; N, 4.09.

7-Isopropoxysulforidazine (**7**).

A stirred mixture of ether **6** (0.42 g, 1.25 mmoles), finely powdered sodium hydroxide (0.2 g, 5 mmoles) and anhydrous toluene (18 ml) was refluxed under nitrogen for 7 hours to produce a dark reaction mixture. Next, 2-(2-chloroethyl)-1-methylpiperidine hydrochloride [19] (0.237 g, 1.37 mmoles) was added to the reaction mixture followed by refluxing for 3 hours. After washing with water (3 x 10 ml), the organic phase was evaporated to dryness under reduced pressure to afford a dark brown product which was purified by silica gel column chromatography using 2% methanol in toluene as the eluent. The fractions homogeneous by tlc were pooled and evaporated to dryness to afford 0.37 g (64%) of **7** as a thick yellow oil which solidified after drying under vacuum, mp 53-55° (with preliminary softening); ^{1}H nmr (DMSO-d_6): δ 1.21 [s, 3H, $(CH_3)_2CH$], 1.22 [s, 3H, $(CH_3)_2CH$], 1.14-2.06 (m, 10H, four piperidine CH_2 and piperidinyl CH_2), 2.10 (s, 3H, NCH_3), 2.71 (m, 1H, methine CH), 3.21 (s, 3H, SO_2CH_3), 3.88 (m, 2H, phenothiazinyl CH_2), 4.52 [sept., 1H, $(CH_3)_2CH$], 6.79 (d, 1H, 6-H, J_m = 2.72 Hz), 6.82 (dd, 1H, 8-H, J_o = 8.68 Hz, J_m = 2.80 Hz), 6.95 (d, 1H, 9-H, J_o = 8.76 Hz), 7.34 (d, 1H, 1-H, J_m = 1.56 Hz), 7.38 (d, 1H, 4-H, J_o = 7.96 Hz), 7.42 (dd, 1H, 3-H, J_o = 8.0 Hz, J_m = 1.64 Hz); ms: m/z 460 (M^+, 1).

Anal. Calcd. for $C_{24}H_{32}N_2O_3S_2 \cdot 0.5H_2O$: C, 61.37; H, 7.08; N, 5.96. Found: C, 61.23; H, 6.88; N, 5.66.

7-Hydroxysulforidazine (**2b**).

Compound **7** (0.1 g, 0.22 mmole) was stirred with 1 *M* boron trichloride in dichloromethane (5 ml) at 0° for 2 hours and then at 25° for 1 hour. The reaction was terminated by the dropwise addition of 2 ml of water with stirring, then the *p*H of the reaction mixture was adjusted to 8.5 (1 *N* sodium hydroxide). The reaction mixture was stirred at 25° for 10 minutes and then extracted with ether (3 x 20 ml). The combined ether extracts were dried over sodium sulfate for 1 hour, filtered and evaporated to dryness to afford 0.065 g of crude product. This was purified on a silica gel column (1.5 x 12 cm) by eluting with 5% methanol in toluene. Appropriate fractions were pooled and evaporated to afford 0.55 g (60%) of **2b**, mp 98-100° (with preliminary softening); ^{1}H nmr (DMSO-d_6): δ 1.14-2.06 (m, 10H, four piperidine CH_2 and piperidinyl CH_2), 2.09 (s, 3H, NCH_3), 2.71 (m, 1H, methine CH), 3.20 (s, 3H, SO_2CH_3), 3.87 (m, 2H, phenothiazinyl CH_2), 6.60 (d, 1H, 6-H, J_m = 2.75 Hz), 6.66 (dd, 1H, 8-H, J_o = 8.73 Hz, J_m = 2.75 Hz), 6.87 (d, 1H, 9-H, J_o = 8.76 Hz), 7.32 (d, 1H, 1-H, J_m = 1.54 Hz), 7.37 (d, 1H, 4-H, J_o = 7.95 Hz), 7.40 (dd, 1H, 3-H, J_o = 7.97 Hz, J_m = 1.57 Hz); ms: m/z 418 (M^+, 2), 293 (1), 227 (1), 126 (6), 112 (2), 99 (8), 98 (100), 70 (14).

Anal. Calcd. for $C_{21}H_{26}N_2O_3S_2 \cdot 0.5H_2O$: C, 58.99; H, 6.36; N, 6.55. Found: C, 58.77; H, 6.46; N, 6.24.

7-Isopropoxythioridazine (**8**).

Sulfone **7** (0.1 g, 0.22 mmole) was stirred in dry toluene (5 ml) under nitrogen and 1.06 ml of 1.5 *M* diisobutylaluminium hydride (DIBAL) (1.6 mmoles) in toluene was added then this was refluxed under nitrogen for 20 hours. After quenching with water (5 ml), the product was extracted with ether (3 x 15 ml). The combined extracts were dried over sodium sulfate, filtered and evaporated *in vacuo* to afford a light yellowish oil which solidified after drying to give 0.068 g (74%) of **8**. This contained a small percent of the deprotected product **2a** and thus it was used without further purification for the subsequent synthesis of **2a**; ^{1}H nmr (DMSO-d_6): δ 1.20 [s, 3H, $(CH_3)_2CH$)], 1.22 [s, 3H, $(CH_3)_2CH$)], 1.14-2.07 (m, 10H, four piperidine CH_2 and piperidinyl CH_2), 2.09 (s, 3H, NCH_3), 2.46 (s, 3H, SCH_3), 2.71 (m, 1H, methine CH), 3.82 (m, 2H, phenothiazinyl CH_2), 4.49 [sept., 1H, $(CH_3)_2CH$], 6.73-7.09 (m, 6H, ArH); ms: m/z 428 (M^+, 1).

7-Hydroxythioridazine (**2a**).

Ether **8** (0.05 g, 0.117 mmole) was stirred with 1 *M* boron trichloride in dichloromethane (3 ml) at 0° for 2 hours, and then at 25° for 18 hours. After addition of water (1 ml) and *p*H adjustment to 8.5 (1*N* sodium hydroxide), the reaction mixture was extracted with ether (3 x 10 ml). Evaporation *in vacuo* of the combined organic phases (sodium sulfate) yielded a crude product which was purified on a silica gel column (1.5 x 13 cm) by eluting with 2% methanol in toluene after initial flushing with toluene. This provided 0.029 g (64%) of the light yellowish solid **2a**, mp 76-77° (with preliminary softening); ^{1}H nmr (DMSO-d_6 + deuterium oxide): δ 1.14-2.07 (m, 10H, four piperidine CH_2 and piperidinyl CH_2), 2.08 (s, 3H, N-CH_3), 2.45 (s, 3H, SCH_3), 2.71 (m, 1H, methine CH), 3.80 (m, 2H, phenothiazinyl CH_2), 6.58 (d, 1H, 6-H, J_m = 2.73 Hz), 6.62 (dd, 1H, 8-H, J_o = 8.61 Hz, J_m = 2.76 Hz), 6.78 (d, 1H, 1-H, J_m = 1.54 Hz), 6.79 (dd, 1H, 3-H, J_o = 7.85 Hz, J_m = 1.84 Hz), 6.82 (d, 1H, 9-H, J_o = 8.69 Hz), 7.05 (d, 1H, 4-H, J_o = 7.87 Hz); ms: m/z 386 (M^+, 5), 275 (2), 126 (13), 125 (3), 99 (8), 98 (100), 70 (15).

Anal. Calcd. for $C_{21}H_{26}N_2OS_2$: C, 65.25; H, 6.78; N, 7.24. Found: C, 65.03; H, 6.95; N, 6.90.

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