SYNTHESIS OF DEUTERIUM LABELLED THIORIDAZINE*

T. Mohammad, K. K. Midha and E. M. Hawes**
College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, S7N 0W0, Canada

SUMMARY

A seven step synthetic route to (±)-10-[2-(1-methyl-2-piperidinyl)ethyl]-2-methylthio-10H-phenothiazine (thioridazine) was developed starting from racemic ethyl 1-methyl-2-piperidinecarboxylate. The lithium aluminum deuteride reduction of the starting and homologous esters allowed the incorporation of deuterium in the 1-and/or 2-position(s) of the ethyl side chain of thioridazine. The isotopic purity of the tetradeuterated and two dideuterated products was greater than 99%.

Key Words: Antipsychotic, thioridazine, deuterium labelling

INTRODUCTION

The phenothiazine antipsychotic agents are generally classified into three types according to the chemical nature of the side chain attached to the nitrogen atom, namely, the dimethylaminopropyl, piperazine and piperidine types. Previously various deuterated analogues of the dimethylaminopropyl (1,2) and piperazine (3-7) types of compounds have been synthesized. No such synthetic report is known to these authors to the piperidine type of compounds, such as thioridazine (Scheme, 9a; Mellaril®). Such deuterated analogues are required for use in metabolic and pharmacokinetic studies and as true internal standards for GC-MS assays (8). In the present study, a synthetic route to thioridazine was developed which allows for the incorporation of up to four deuterium atoms in its metabolically inert N-10 ethyl side chain. The syntheses of 1,1-$^2H_2$ (9b), 2,2-$^2H_2$ (9c) and 1,1,2,2-$^2H_4$ (9d) labelled thioridazine are reported.

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**To whom correspondence should be addressed

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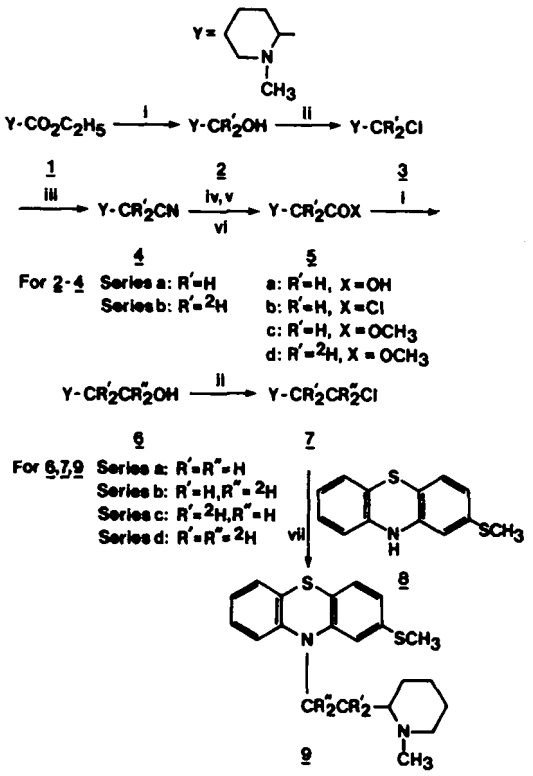
DISCUSSION

Synthetic routes to thioridazine were investigated in which lithium aluminum deuteride (LAD) or deuterated borane could be utilised to incorporate deuterium in the N-10 ethyl side chain of the thioridazine structure (Scheme). A convenient starting material in this investigation was the commercially available compound, racemic ethyl 1-methyl-2-piperidinecarboxylate (1). Indeed, lithium aluminum hydride (LAH) reduction of this ester 1 gave the carbinol 2a. There are previous reports (9,10) to the reduction of an ester of 1-methyl-2-piperidinecarboxylic acid with aluminohydrides to obtain the intermediate aldehyde as the major product. Treatment of the carbinol 2a with thionyl chloride provided the previously reported (11) chloro compound 3a, which in turn by reaction with KCN in DMSO was converted to the corresponding nitrile 4a. This previously unreported nitrile was subsequently hydrolysed to the acid 5a and methyl ester 5c, with a view to investigate the most appropriate intermediate for use in the subsequent steps of the synthetic route to obtain thioridazine. Earlier workers (12-14) reported that the ester 5c was obtained by catalytic hydrogenation of 1-methyl-2-methoxycarbonylmethylpyridinium salts.

The synthetic route to thioridazine (9a), first planned to be investigated, involved acylation of 2-methylthio-10H-phenothiazine (8) with the acid chloride 5b, prepared from the acid 5a, and subsequent reduction of the amide product 9 (R'=H, R_2'' =O) with borane (15). Unfortunately, all attempts to acylate 8 with freshly prepared acid chloride 5b, under a variety of conditions, failed to provide the amide. In every case the phenothiazine 8 was recovered unchanged, likely because the acid chloride 5b decomposed to a number of unidentified products. It is noteworthy that a similar thermal instability has been observed for the 3-isomer of 5b (16).

In view of the failure of the route to thioridazine via the amide 9 (R'=H, R_2''=O), an alternative route via the acid 5a or the ester 5c was investigated. Reduction of either of these intermediates with LAH gave the carbinol 6a, however, the yield was higher with the ester 5c as substrate. The carbinol 6a was previously reported by the catalytic reduction of the corresponding pyridinium methochloride (17). Subsequently, treatment of the carbinol 6a with thionyl

Scheme: Synthesis of deuterium labelled thioridazine



Reagents: i) $LiAlH_4$ or $LiAl^2H_4$, $(C_2H_5)_2O$
ii) $SOCl_2$, $CHCl_3$, Δ iii) KCN, DMSO
iv) KOH, C_2H_5OH, H_2O v) $SOCl_2$, $CHCl_3$
vi) HCl gas, CH_3OH vii) NaOH, $PhCH_3$

chloride produced the chloro compound 7a. Finally, N-10 alkylation of 2-methylthio-10H-phenothiazine (8) with 7a gave (±)-thioridazine (9a). The reaction conditions used in this alkylation were adapted from a patented procedure (18) for the synthesis of the 2-methylsulfinyl analogue of 9a.

By substitution of LAD for LAH in the appropriate step(s), the above synthetic route to thioridazine was adapted to incorporate deuterium in the 1- and/or 2-position(s) of the ethyl side chain. Thus, 1,1-$^2H_2$ (9b), 2,2-$^2H_2$ (9c) and 1,1,2,2-$^2H_4$ (9d) labelled (±)-thioridazine were respectively obtained as outlined in the Scheme: 1 → 2a → 3a → 4a → 5c → 6b → 7b → 9b; 1 → 2b → 3b → 4b → 5d → 6c → 7c → 9c; and 1 → 2b → 3b → 4b → 5d → 6d → 7d → 9d. For each of the seven steps involved in these syntheses yields were at least 70%.

The isotopic purity of the labelled purified products was determined by electron impact mass spectrometry. The ratios for the molecular ions $^{2}H_{0}/^{2}H_{n}$ were found to be 3.66, 1.50 and 1.07% for 9b, 9c and 9d, respectively. Correction of these ratios for the $M^{+\cdot}$-2 or $M^{+\cdot}$-4 ions originating from nondeuterated thioridazine indicated that the isotopic purity of each variant was greater than 99%. This purity is sufficient for the use of these isotopomers of thioridazine in metabolic and pharmacokinetic studies, as well as true internal standards in GC-MS assays.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Observed boiling points are also uncorrected. Literature melting points and boiling points refer to the nondeuterated compounds. TLC was carried out on pre-coated fluorescent plates of 0.2 mm thickness (Kieselgel 60 F_{254}; E. Merck) and spots were visualized under shortwave UV light and/or iodine vapour. Column chromatography was performed using Baker silica gel 60-200 mesh. IR spectra were recorded on Perkin-Elmer 297 and/or Beckman Acculab 4 infrared spectrophotometers, as thin films for liquids and KBr disks for solids. ^{1}H NMR spectra were measured on a Varian T-60 spectrometer in deuteriochloroform; chemical shift values are expressed in δ units (parts per million) downfield from tetramethylsilane as an internal standard; and in situations where multiplets could not be measured easily, the centre of gravity was taken as the chemical shift. Low resolution electron impact mass spectra (EIMS) were recorded on a Vg Micromass 7070HE instrument at 70 eV equipped with a Vg 2035 data system; relative intensity is noted in parentheses after each fragment. Elemental analyses for samples dried over phosphorus pentoxide at 60°C under reduced pressure were performed by Guelph Chemical Laboratories, Ltd., Guelph, Ontario. All organic extracts were dried over anhydrous sodium sulfate. The removal of solvent from crude reaction mixtures was carried out on a Büchi Rotavapor-R connected to a water aspirator. LAD (>99% deuterium) was obtained from Merck, Sharp and Dohme, Dorval, Quebec. All other chemicals were procured from Aldrich Chemical Co., Milwaukee, WI.

2-Hydroxymethyl-1-methylpiperidine (2a): To a stirred suspension of LAH (2.85 g, 75 mmol) in anhydrous ether (150 mL), ethyl ester 1 (8.55 g, 50 mmol) in ether (50 mL) was added slowly during a 30 min period. After the addition was over, the reaction mixture was refluxed for 6 h. Excess LAH was decomposed cautiously with cold water, followed by the addition of 20% aqueous NaOH (20 mL) and the reaction mixture was allowed to stand overnight. The organic layer was decanted off and the white residual cake was extracted with fresh ether (3 x 40 mL). The combined ether extracts were washed with brine and dried. The solvent was stripped off on a rotavapor to leave the carbinol 2a as a pure viscous oil (6.0 g, 93%). The identity of the product was confirmed by TLC, co-TLC and ^{1}H NMR comparisons with an authentic commercial sample.

2-Hydroxy[$^2H_2$]methyl-1-methylpiperidine (2b): This was prepared by LAD reduction of 1 using the method described for 2a, IR: 3300 cm^{-1} (O-H); ^{1}H NMR: 1.33-2.17(m,8H,piperidine C$\underline{H}_2$), 2.33(s,3H,NC$\underline{H}_3$), 2.90(m,1H,methine $\underline{H}$), 3.57(s,1H,O$\underline{H}$,D_2O exchangeable); EIMS:m/z 131(0.3,$M^{+\cdot}$), 98(100).

2-Chloromethyl-1-methylpiperidine (3a): A solution of the carbinol 2a (5.0 g, 39 mmol) in anhydrous chloroform (25 mL) at 0°C was saturated with dry HCl gas. Thionyl chloride (6.9 g, 58 mmol) was added dropwise. After the addition was over, the solution was refluxed on a steam bath for 3 h. The solvent and excess thionyl chloride were removed on a rotavapor and the solid was triturated with ether. Recrystallization of the solid from acetone afforded white needles of the hydrochloride salt of 3a (5.85 g, 82%), mp 161-163°C [lit. (11) mp 159-161°C]. The free base obtained on basification of an aqueous solution of the hydrochloride salt with Na_2CO_3 distilled as a colourless liquid at 66-68°C/12 mm Hg; ^{1}H NMR(free base): 1.17-2.17(m,8H,piperidine C$\underline{H}_2$), 2.33(s,3H,NC$\underline{H}_3$), 2.87(m,1H,methine $\underline{H}$), 3.60(m,2H,C$\underline{H}_2$Cl); EIMS:m/z 149/147(1/3,$M^{+\cdot}$), 98(100).

2-Chloro[$^2H_2$]methyl-1-methylpiperidine (3b): This was prepared from the carbinol 2b using the method described for 3a, mp of hydrochloride salt 158-160°C, an admixture mp with authentic nondeuterated hydrochloride salt of 3a was not depressed; ^{1}H NMR(free base): 1.17-2.17(m,8H,piperidine C$\underline{H}_2$),

2.33(s,3H,NCH_3), 2.87(m,1H,methine H); EIMS:m/z 151/149(1/3,$M^{+\cdot}$), 98(100).

2-Cyanomethyl-1-methylpiperidine (4a): A stirred mixture of the chloro compound 3a (5.0 g, 34 mmol) and KCN (4.4 g, 68 mmol) in anhydrous DMSO (25 mL) (dried over molecular sieves Type 4A) was heated at 60-70°C for 15 h. After cooling to room temperature, the reaction mixture was diluted with water (150 mL) and 5% aqueous NaOH solution added. The aqueous phase was extracted with methylene chloride and the combined organic extracts were washed with brine and dried. The solvent was removed on a rotavapor to afford an oil, which distilled *in vacuo* to give the nitrile 4a as a colourless liquid (3.8 g, 81%), bp 77-78°C/0.2 mmHg; IR: 2250 cm^{-1} (C≡N); ^1H NMR: 1.07-2.00(m,8H,piperidine CH_2 and CH_2CN), 2.27(s,3H,NCH_3), 2.50(t,J=5Hz,2H,piperidine NCH_2), 2.84(m,1H,methine H); EIMS:m/z 138(13,$M^{+\cdot}$), 98(100). Anal. Calcd. for $C_8H_{14}N_2$: C,69.57; H,10.14; N,20.29. Found: C,69.78; H,10.51; N,20.12.

2-Cyano[$^2H_2$]methyl-1-methylpiperidine (4b): This was prepared from the chloro compound 3b by the same procedure as for 4a, bp 76-77°C/0.15 mmHg; IR:2250 cm^{-1} (C≡N); ^1H NMR: 1.63(br s,6H,piperidine CH_2), 2.07-2.50(m containing NCH_3 spike at 2.30,5H,NCH_3 and piperidine NCH_2), 2.83(m,1H,methine H); EIMS:m/z 140(4,$M^{+\cdot}$), 98(100).

1-Methyl-2-piperidinylacetic acid (5a): A stirred mixture of the nitrile 4a (1.4 g, 10 mmol), ethanol (7 mL), KOH (2.24 g, 40 mmol) and water (3 mL) was refluxed in an oil bath for 36 h. The solution was concentrated *in vacuo* and the residue, dissolved in water (50 mL), was acidified with concentrated H_2SO_4 while cooling the flask in an ice-bath. The solution was made basic with saturated $Ba(OH)_2$ solution, excess barium precipitated with CO_2 gas and the mixture filtered through celite. The filtrate was evaporated on a rotavapor and the residue, dissolved in methylene chloride, was filtered and dried. Removal of solvent on a rotavapor gave an oil which solidified *in vacuo*. Recrystallization from acetonitrile provided the acid 5a as a white solid (1.11 g, 69.8%), mp 140-141°C; R_f(n-BuOH:AcOH:H_2O, 4:2:1)0.24. A small sample was converted into the hydrochloride salt of 5a, mp 162-164°C (methanol-ether); R_f(solvent system as above)0.20; IR: 1725 cm^{-1}(C=O); ^1H NMR(free acid): 1.83(br s,6H,piperidine CH_2), 2.67(br s,5H,NCH_3 and CH_2CO), 2.83-

3.60(m,3H,piperidine NC$\underline{H}_2$ and methine $\underline{H}$), 12.23(br s,1H,O$\underline{H}$,D_2O exchangeable); EIMS:m/z 157(37,$M^{+\cdot}$), 98(100). Anal. Calcd. for $C_8H_{15}NO_2$: C,61.14; H,9.55; N,8.92. Found: C,60.89; H,9.38; N,9.10.

Attempted synthesis of 10-(1-Methyl-2-piperidinylacetyl)-2-methylthio-10$\underline{H}$-phenothiazine (9, R'=H; R''=O): To an ice-cooled solution of the acid 5a (175 mg, 1.1 mmol) in anhydrous chloroform (2 mL), thionyl chloride (0.6 mL) was added dropwise. The resultant solution was subsequently stirred at ambient temperature for 4 h, where upon a slight pink colour developed. The solution was concentrated on a rotavapor at 40°C to leave a light brick red residual solid of the hydrochloride salt of the acid chloride 5b, which was sufficiently pure for use in the subsequent step, IR: 1795 cm^{-1} (C=O).

To a suspension of 5b hydrochloride in anhydrous benzene (5 mL) was added 2-methylthio-10$\underline{H}$-phenothiazine (8, 245 mg, 1.0 mmol) followed by dry pyridine (0.16 mL, 2.0 mmol). The resultant reddish brown solution was heated at reflux for 16 h. After allowing the reaction mixture to cool to room temperature, the organic phase was extracted successively with water, 5% $NaHCO_3$ solution and water and dried. Removal of solvent on a rotavapor and crystallization of the residue from benzene provided a solid which was found to be identical with authentic 8 (TLC, co-TLC; mp, admixture mp). The mother liquor showed a number of spots on TLC (benzene:ethanol, 1:1).

Methyl 1-methyl-2-piperidinylacetate (5c): A solution of the nitrile 4a (5.0 g) in anhydrous methanol (100 mL) at 0 to -5°C was saturated with dry HCl gas. The mixture was left in the refrigerator overnight and then poured onto crushed ice (400 g) and stirred for 3 h. The solution was basified with saturated Na_2CO_3 solution and then saturated with NaCl. The aqueous phase was extracted thoroughly with methylene chloride. The combined organic extracts were washed with brine and dried. The solvent was removed on a rotavapor and the resultant oil distilled *in vacuo* to give the ester 5c as a colourless liquid (4.4 g, 71%), bp 76-77°C/3.5 mmHg [lit. (13) bp 119-121°C/29 mmHg]; IR: 1740 cm^{-1} (C=O); ^1H NMR: 1.67(br s,6H,piperidine C$\underline{H}_2$), 2.20-3.00(m containing NCH_3 spike at 2.30,8H,N$\underline{CH}_3$, piperidine NC$\underline{H}_2$,methine $\underline{H}$ and C$\underline{H}_2$CO),

3.73(s,3H,OCH_3); EIMS:m/z 171(5,$M^{+\cdot}$), 98(100). Anal. Calcd. for $C_9H_{17}NO_2$: C,63.15; H,9.94; N,8.19. Found: C,62.68; H,10.08; N,8.33.

Methyl 1-methyl-2-piperidinyl[$^2H_2$]acetate (5d): This was prepared from 4b by the same procedure as for 5c, IR: 1740 cm^{-1} (C=O); ^1H NMR: 1.60(br s,6H, piperidine CH_2), 2.17-2.97(m containing NCH_3 spike at 2.30,6H,NCH_3,piperidine NCH_2 and methine H); 3.70(s,3H,OCH_3); EIMS:m/z 173(15,$M^{+\cdot}$), 98(100).

2-(2-Hydroxyethyl)-1-methylpiperidine (6a): (i) - From the ester 5c. A solution of the ester 5c (3.42 g, 20 mmol) in anhydrous ether (20 mL) was added slowly to a stirred suspension of LAH (1.14 g, 30 mmol) in anhydrous ether (70 mL). The reaction mixture was then treated and worked up as in the preparation of 2a. The oil obtained was distilled *in vacuo* to give the carbinol 6a as a colourless liquid (2.63 g, 92%), bp 62-63°C/0.6 mmHg [lit. (17) bp 80°C/2 mmHg]; IR: 3300 cm^{-1}(O-H); ^1H NMR: 1.33-2.30(m,10H,piperidine CH_2 and piperidinyl CH_2), 2.37(s,3H,NCH_3), 2.83(m,1H,methine H), 3.83(m,2H,CH_2OH), 4.40(br s,1H,OH,D_2O exchangeable); EIMS:m/z 143(4,$M^{+\cdot}$), 98(100).

(ii) - From the acid 5a. The acid 5a (0.942 g, 6 mmol) was placed in the thimble of a Soxhlet extractor. The reaction flask was charged with LAH (0.456 g, 12 mmol) in 150 mL of anhydrous ether. The stirred slurry was refluxed for 48 h. The reaction mixture was then worked up as in (i) to provide the carbinol 6a [0.6 g, 70% (76%, based on recovered starting acid 5a)].

2-(2-Hydroxy[1,1-$^2H_2$]ethyl)-1-methylpiperidine (6b): This carbinol was prepared by use of LAD in the method (i) from the ester 5c, TLC and co-TLC as for 6a; IR: 3300 cm^{-1} (O-H); ^1H NMR: 1.17-2.30(m,10H,piperidine CH_2 and piperidinyl CH_2), 2.37(s,3H,NCH_3), 2.87(m,1H,methine H), 4.00(br s,1H,OH); EIMS:m/z 145(11,$M^{+\cdot}$), 98(100).

2-(2-Hydroxy[2,2-$^2H_2$]ethyl)-1-methylpiperidine (6c): This carbinol was prepared from the ester 5d and LAH using the procedure (i) described for 6a, TLC and co-TLC as for 6a: IR:3300 cm^{-1} (O-H); ^1H NMR: 1.20-2.27(m,8H,piperidine CH_2), 2.37(s,3H,NCH_3), 2.90(m,1H,methine H), 3.77(m,2H,CH_2OH), 4.17(br s,1H, OH,D_2O exchangeable); EIMS:m/z 145(3,$M^{+\cdot}$), 98(100).

2-(2-Hydroxy[1,1,2,2-$^2H_4$]ethyl)-1-methylpiperidine (6d): This was prepared from the ester 5d and LAD using the procedure described for 6a, TLC and co-TLC

as for 6a; IR: 3300 cm^{-1} (O-H); ^1H NMR: 1.17-2.30(m,8H,piperidine CH_2), 2.37 (s,3H,NCH_3), 2.87(m,1H,methine H), 4.00(br s,1H,OH,D_2O exchangeable); EIMS:m/z 147(10,$M^{+\cdot}$), 98(100).

2-(2-Chloroethyl)-1-methylpiperidine (7a): Dry HCl gas was passed through a solution of the carbinol 6a (2.5 g, 17 mmol) in anhydrous chloroform (15 ml) at 0°C till saturation. While continuing cooling, thionyl chloride (3.0 g, 25 mmol) was dropped in slowly with stirring. The resultant solution was subsequently handled as for the preparation of 3a, to obtain a residual solid, which was then dissolved in 25% aqueous HCl (125 ml) and treated with activated charcoal. The filtered solution was evaporated to dryness on a rotavapor and the solid so obtained was recrystallized from acetone as white crystals of 7a hydrochloride (3.01 g, 87%), mp 131-32°C [lit.(17) mp 132-33°C]; ^1H NMR(free base): 1.17-2.23(m,10H,piperidine CH_2 and piperidinyl CH_2), 2.33(s,3H,NCH_3), 2.83(m,1H,methine H), 3.67(m,2H,CH_2Cl); EIMS:m/z 163/161(1/3,$M^{+\cdot}$), 98(100).

2-(2-Chloro[1,1-$^2H_2$]ethyl)-1-methylpiperidine (7b): This was prepared from the carbinol 6b using the method described for 7a, mp and admixture mp with nondeuterated hydrochloride salt as for 7a; ^1H NMR(free base): 1.17-2.17(m,10H,piperidine CH_2 and piperidinyl CH_2), 2.33(s,3H,NCH_3), 2.87(m,1H, methine H); EIMS:m/z 165/163(2/6,$M^{+\cdot}$), 98(100).

2-(2-Chloro[2,2-$^2H_2$]ethyl)-1-methylpiperidine (7c): This was prepared from the carbinol 6c using the method described for 7a, mp and admixture mp with nondeuterated hydrochloride salt as for 7a; ^1H NMR(free base): 1.00-2.17(m,8H, piperidine CH_2), 2.30(s,3H,NCH_3), 2.83(m,1H,methine H), 3.60(br s,2H,CH_2Cl); EIMS:m/z 165/163(1/3,$M^{+\cdot}$), 98(100).

2-(2-Chloro[1,1,2,2-$^2H_4$]ethyl)-1-methylpiperidine (7d): This was prepared from the carbinol 6d using the method described for 7a, mp and admixture mp with nondeuterated hydrochloride salt as for 7a; ^1H NMR(free base): 1.17-2.13(m,8H, piperidine CH_2), 2.23(s,3H,NCH_3), 2.83(m,1H,methine H); EIMS:m/z 167/165(2/7, $M^{+\cdot}$), 98(100).

10-[2-(1-Methyl-2-piperidinyl)ethyl]-2-methylthio-10H-phenothiazine (Thioridazine) (9a): A stirred mixture of 2-methylthio-10H-phenothiazine (8, 0.49 g, 2

mmol), finely powdered NaOH (0.32 g, 8 mmol) and anhydrous toluene (10 ml) (dried over molecular sieves Type 5A) was refluxed in an atmosphere of nitrogen in the absence of direct intense light. After 5h reflux, a light yellow colour solution was produced and the chloro compound 7a (0.435 g, 2.2 mmol) was added slowly in small portions over a period of 1 h while continuing the refluxing. The resultant almost colourless solution was refluxed for an additional 3h. The reaction mixture was cooled and the organic phase was washed with water and then extracted with dilute HCl. The combined acid extracts were basified with NaOH and then extracted with methylene chloride. The combined organic extracts were washed with water, dried and evaporated on a rotavapor. The resultant oily residue was chromatographed over silica gel to obtain thioridazine (9a, 0.563 g, 76%), which was found to be identical with an authentic commercial sample by comparison of TLC and co-TLC in a number of solvent systems and spectral correlation; ^{1}H NMR: 1.17-2.07(m,10H,piperidine CH_2 and piperidinyl CH_2), 2.20(s,3H,NCH_3), 2.40(s,3H,SCH_3), 2.83(m,1H,methine H), 3.87(m,2H,phenothiazinyl CH_2), 6.67-7.27(m,7H,ArH); EIMS:m/z 370(29,$M^{+\cdot}$), 98(100). The oil was treated with ethereal HCl and the solid so obtained was recrystallised from acetone as white crystals of 9a hydrochloride, mp 157-59° [lit. (19) mp 158-60°C], and admixture with the authentic commercial sample (mp 156-58°C) did not show any depression.

10-[2-(1-Methyl-2-piperidinyl)[1,1-$^2H_2$]ethyl]-2-methylthio-10H-phenothiazine (9b): This was prepared from 8 and the chloro compound 7b by the method described for 9a, TLC, co-TLC and mp and admixture mp of the hydrochloride salt as for 9a; ^{1}H NMR(free base): 1.17-2.07(m,10H,piperidine CH_2 and piperidinyl CH_2), 2.20(s,3H,NCH_3), 2.42(s,3H,SCH_3), 2.83(m,1H,methine H), 6.67-7.30 (m,7H,ArH); EIMS:m/z 372(17,$M^{+\cdot}$), 98(100).

10-[2-(1-Methyl-2-piperidinyl)[2,2-$^2H_2$]ethyl]-2-methylthio-10H-phenothiazine (9c): This was prepared from 8 and the chloro compound 7c by the method described for 9a, TLC, co-TLC and mp and admixture mp of the hydrochloride salt as for 9a; ^{1}H NMR(free base): 1.00-2.13(m,8H,piperidine CH_2), 2.20(s,3H,NCH_3),

2.43(s,3H,SC$\underline{H}_3$), 2.80(m,1H,methine $\underline{H}$), 3.87(br s,2H,phenothiazinyl C$\underline{H}_2$), 6.67-7.33(m,7H,Ar$\underline{H}$); EIMS:m/z 372(25,$M^{+\cdot}$), 98(100).

10-[2-(1-Methyl-2-piperidinyl)[1,1,2,2-$^2H_4$]ethyl]-2-methylthio-10$\underline{H}$-phenothiazine (9d): This was prepared from 8 and the chloro compound 7d by the method described for 9a, TLC, co-TLC and mp and admixture mp of the hydrochloride salt as for 9a; ^{1}H NMR(free base): 1.17-2.10(m,8H,piperidine C$\underline{H}_2$), 2.20(s,3H,NC$\underline{H}_3$), 2.43(s,3H,SC$\underline{H}_3$), 2.83(m,1H,methine $\underline{H}$), 6.67-7.30(m,7H,Ar$\underline{H}$); EIMS:m/z 374(45,$M^{+\cdot}$), 98(100).

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