SYNTHESIS OF DEUTERIUM LABELLED THIORIDAZINE VIA RUTHENIUM TETROXIDE OXIDATION OF THE PIPERIDINE RING*

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SUMMARY

A multistep synthetic route to (±)-10-[2-(1-methyl-2-piperidinyl)ethyl]-2-methylthio-10H-phenothiazine (thioridazine) was developed which allowed for the incorporation of two deuterium atoms in the piperidine ring and a further two in the 1-position of the ethyl side chain. The key steps involved ruthenium tetroxide oxidation of N-protected methyl 2-piperidinylacetate and subsequent lithium aluminum deuteride reduction of 2-(2-hydroxyethyl)-1-methyl-6-piperidinone or the corresponding piperidinoneester. The isotopic purity of the dideuterated and tetradeuterated products was greater than 99%.

Key Words: Antipsychotic, thioridazine, piperidine ring, deuterium labelling, ruthenium tetroxide oxidation

INTRODUCTION

Thioridazine (Scheme, 9a) is a piperidine type phenothiazine antipsychotic agent with a 2-(1-methyl-2-piperidinyl)ethyl side chain attached to the N-10 position of the phenothiazine ring. Deuterium labelled analogues were required for metabolic and pharmacokinetic studies and as true internal standards for GLC-MS assays. Recently the synthesis was reported of thioridazine with two or four deuterium atoms in the ethyl group of the N-10 side chain (1). This paper describes for the first time the synthesis of a piperidine type of phenothiazine antipsychotic agent with a label in the piperidine ring. Thus, two specifically labelled analogues of thioridazine were synthesized; one with two deuterium atoms solely in the 6-position of the piperidine ring and the other with an additional two deuterium atoms in the 1-position of the ethyl group of the N-10 side chain.

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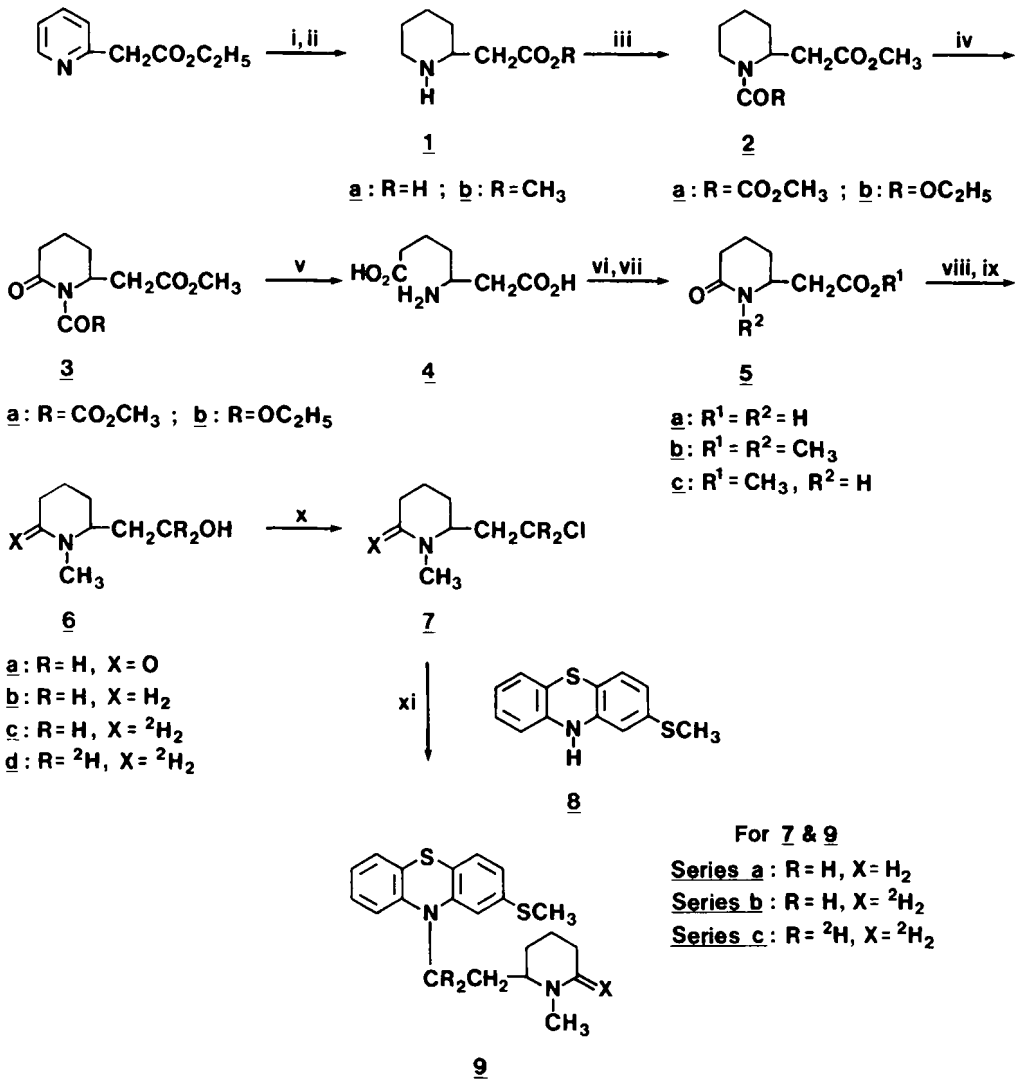
DISCUSSION

An envisaged suitable synthetic sequence to thioridazine which could be adapted to incorporate two deuterium atoms in the piperidine ring involved two key steps: ruthenium tetroxide (RuO_4) oxidation of an N-protected 2-substituted piperidine (e.g., Scheme: 2→3) and at a later stage (e.g. 5→6, where $X=H_2$) lithium aluminum hydride (LAH) reduction of the resultant piperidinone. Ruthenium tetroxide oxidation of acylated cyclic amines to give lactams and/or imides (2) has recently found use in the conversion of 2-substituted piperidines to the analogous piperidinones (3). However, we are unaware of any report to the use of ruthenium tetroxide in a synthetic sequence designed to incorporate a label in the piperidine ring. Also since this oxidizing agent does not affect ester groups it was envisaged that by use of an appropriate N-protected 2-piperidinylacetate in the synthetic route to thioridazine, the route could be adapted to incorporate a further two deuterium atoms in the N-10 ethyl side chain. Hence, the piperidinoneester 5b (Scheme) was considered as an intermediate suitable for the synthesis of both di- and tetradeuterated thioridazine.

The piperidinoneester 5b was synthesized in seven steps from ethyl 2-pyridinylacetate as shown in the Scheme. The use of Ni-Al alloy in aqueous KOH solution in the reduction of various nitrogen heteroaromatics, including pyridines, to the corresponding saturated compounds has been recently reported (4). In fact, using such conditions, ethyl 2-pyridinylacetate was effectively reduced to the corresponding piperidine with concurrent saponification to give the acid 1a. Treatment of the latter with methanolic HCl gave the ester 1b, which was in turn reacted with methyloxalyl chloride or ethyl chloroformate to respectively furnish the N-protected derivatives 2a and 2b. The initial strategy to produce the desired intermediate piperidinoneester 5b was through RuO_4 oxidation of the methyloxalyl derivative 2a to the piperidinone 3a, followed by removal of the protecting group with sodium methoxide in methanol (2) to give 5c. Subsequent N-methylation of 5c would lead to 5b, thus obviating ring cleavage of the resultant piperidinone (vide infra). Unfortunately attempted oxidation of 2a with RuO_4 even under conditions such as use of a large excess of oxidant and an extended reaction time (72 h), resulted in recovery of only the starting material. Contemporary to our observation, Yoshifuji et al. (5) have discussed the unfavourable role of the methyloxalyl group in protecting

Scheme: Synthesis of deuterium labelled thioridazine



Reagents:

i) Ni-Al, KOH, H_2O
ii) HCl gas, CH_3OH
iii) $Cl(CO)_2OCH_3$ or $ClCO_2C_2H_5$, $(C_2H_5)_3N$, C_6H_6
iv) $RuO_2 \cdot xH_2O$, $NaIO_4$, $CH_3CO_2C_2H_5$-H_2O
v) 6N HCl
vi) C_5H_5N
vii) CH_3I, NaH, DMF
viii) $NaBH_4$, CH_3OH-THF
ix) $LiAlH_4$ or $LiAl^2H_4$, $(C_2H_5)_2O$ or THF-$(C_2H_5)_2O$
x) $SOCl_2$, $CHCl_3$
xi) NaOH, $PhCH_3$

cyclic amines in reaction sequences involving RuO_4 oxidation. On the other hand, the ethoxycarbonyl derivative 2b gave the piperidinone 3b in excellent yield when subjected to RuO_4 oxidation which merely involved treatment for 3 h at room temperature with a catalytic amount of ruthenium oxide (RuO_2) and an excess of 10% $NaIO_4$ in a two-phase system of ethyl acetate-water (3). Subsequent treatment of 3b with 6N HCl removed the protecting group and hydrolysed the piperidinone-ester to give β-aminopimelic acid (4), which cyclised to the piperidinoneacid 5a on refluxing in pyridine. Methylation of 5a with iodomethane employing NaH in N,N-dimethylformamide provided the piperidinoneester 5b in high yield. The monomethylated product 5c was obtained as a minor product, even with an extended reaction time and use of a large excess of iodomethane or NaH. However, the presence of 5c did not hamper the purification of the desired piperidinoneester 5b. There have been two previous reports to the synthesis of 5b. Each similarly involved a multistep sequence but completely differed in approach: in that in one, the starting material already contained the ring carbonyl group (6), while in the other, this group was introduced by alkaline potassium ferricyanide oxidation of a 2-substituted N-methylpyridinium salt (7).

With 5b in hand, the remainder of the synthetic reactions to thioridazine were developed with a view as to whether two or four deuterium atoms were to be eventually incorporated in the molecule by means of reduction with lithium aluminum deuteride (LAD). Thus, the ester function of 5b was selectively reduced with sodium borohydride (8) to give the piperidinonealcohol 6a. Subsequent reduction of 6a with LAH provided the piperidinealcohol 6b. This alcohol was also prepared from the piperidinoneester 5b by reduction with LAH. Furthermore, reduction of 3b with LAH gave the same alcohol 6b, thereby providing the means to adapt this route to obtain heptadeuterated thioridazine; a line of investigation not pursued in the present work. The alcohol 6b so produced by the three routes was converted to the chloro compound 7a by treatment with thionyl chloride. Finally, N-10 alkylation of 2-methylthio-10H-phenothiazine (8) with 7a provided (±)-thioridazine (9a), which was found to be identical with an authentic commercial sample (TLC, co-TLC, and EIMS, ^1H and ^{13}C NMR spectra).

By substitution of LAD for LAH in the appropriate above described steps in the conversion of the piperidinoneester 5b to thioridazine, the route was adapted to incorporate deuterium in the 6-position of the piperidine ring and also the

1-position of the N-10 ethyl side chain. Thus, 6,6-$^2H_2$ (9b) and 1,1(ethyl side chain),6,6(piperidine ring)-$^2H_4$ (9c) labelled thioridazine were respectively obtained from 5b as follows: 5b → 6a → 6c → 7b → 9b and 5b → 6d → 7c → 9c. For each of the steps involved in these syntheses, as well as the seven steps involved in the conversion of ethyl 2-pyridinylacetate to 5b, the yield was at least 68%.

The isotopic purity of each labelled purified product was determined by a single ion monitoring technique using electron impact mass spectrometry. The ratios for the molecular ions $^2H_o/^2H_n$ of 9b and 9c were respectively found to be 1.11 and 0.23%. Respective 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 labelled compound was greater than 99%. This isotopic purity is sufficient for the use of these isotopomers of thioridazine in metabolic and pharmacokinetic studies, as well as true internal standards in GLC-MS assays.

EXPERIMENTAL

Melting points (mp) were determined in open capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. Observed boiling points (bp) are also uncorrected. Literature mp and bp refer to the nondeuterated compounds. Thin layer chromatography (TLC) was performed 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 vapours. Column chromatography was performed using Baker silica gel 60-200 mesh. IR spectra were recorded on a Beckman Acculab 4 infrared spectrophotometer, as thin films for liquids and KBr disks for solids. ^1H and ^{13}C NMR spectra were respectively measured in deuteriochloroform (unless otherwise specified) on Varian T-60 (60 MHz) or Bruker AM-300 (300.13 MHz) and Bruker AM-300 (75.5 MHz) spectrometers. Chemical shift values are expressed (^1H in δ units and ^{13}C in ppm) relative to internal tetramethylsilane at δ 0.00 ppm. In situations where multiplets of ^1H NMR spectra could not be measured easily, the center of gravity was taken as the chemical shift. For ^{13}C NMR spectra, a shift assigned as a carbon-deuterium quintet (q) corresponds to the central peak. Low resolution electron impact mass spectra (EIMS) of probe samples were recorded on a Vg Micromass 7070HE instrument at 70 eV coupled to a Vg 2035 data system; relative intensity is noted in parentheses after each fragment. Fast atom bombardment mass spectrum (FAB MS) was obtained in a matrix of

glycerol with a potential of 6 keV applied to the argon gun. 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. Unless otherwise specified, all other chemicals were procured from Aldrich Chemical Co., Milwaukee, Wi. Ether refers to diethyl ether.

2-Piperidinylacetic acid (1a): To a stirred solution of ethyl 2-pyridinylacetate (10.0 g) in distilled water (200 mL) containing 1M KOH solution (200 mL), Ni-Al alloy (50.0 g) (BDH Chemical Co.) was added in portions over a period of 1 h (in an efficient hood and in absence of any flame). After the addition was complete, stirring was continued at room temperature for 24 h. The contents of the flask were filtered through celite and the residue was washed with a further portion of water (200 mL). (Before disposal the nickel so removed was allowed to dry for 24 h on a stainless steel tray in the absence of flammable solvents). The combined filtrate was carefully acidified with concentrated H_2SO_4 while cooling the flask in an ice bath. The solution was then basified with saturated $Ba(OH)_2$ solution, excess barium precipitated with CO_2 gas and the mixture filtered through celite. The filtrate was evaporated to dryness on a rotavapor and the residual solid was extracted with CH_3OH. Evaporation of solvent gave pure white acid 1a (6.40 g, 74%). An analytical sample was obtained by recrystallization from methanol-ether as colourless needles, mp 213-214°C [lit. (9) mp 212°C]; IR(hydrochloride salt): 1735 cm^{-1}(C=O); ^1H NMR(free acid)(C^2HCl_3 and a trace of $C^2H_3O^2H$)(60 MHz): 1.77(br s,6H,C_3-H_2,C_4-H_2,C_5-H_2), 2.45(m,2H,$C\underline{H}_2CO$), 2.67-3.67 (m,3H,C_2-H,C_6-H_2); EIMS:m/z 143(3,$M^{+\cdot}$), 99(1), 98(1), 84(100), 60(7), 56(19), 45(2). Anal. Calcd. for $C_7H_{13}NO_2$: C,58.72; H,9.15; N,9.78. Found: C,58.59; H,9.46; N,9.96.

Methyl 2-piperidinylacetate (1b): A few drops of freshly prepared methanolic HCl were added to the acid 1a (5.0 g) suspended in CH_3OH (25 mL) and the resultant clear solution was transferred to the remainder of the methanolic HCl (75 mL) at 0°C. The solution was stirred at 0°C for 1 h, then heated at reflux for 15 h. The cooled solution was basified with anhydrous Na_2CO_3, filtered and the residue washed with CH_3OH. The combined filtrate was evaporated to dryness on a rota-

vapor at 40-50°C. The residual oil was extracted into ether and evaporation of solvent on a rotavapor afforded the pure ester 1b (3.75 g, 68%), which distilled as a colourless liquid at 57-58°C/0.65 mmHg [lit. (10) bp 101-103°C/16 mmHg]; IR: 3350(N-H), 1740 cm^{-1}(C=O); ^{1}H NMR(60 MHz): 0.93-1.93(m,6H,C_3-H_2,C_4-H_2,C_5-H_2), 2.20-3.23(m,6H,C_2-H,C_6-H_2,CH_2CO,NH), 3.70(s,3H,OCH_3); EIMS:m/z 157(15, $M^{+\cdot}$), 126(1), 98(7), 84(100), 74(16), 59(6), 56(38), 43(5). Anal. Calcd. for $C_8H_{15}NO_2$: C,61.12; H,9.62; N,8.91. Found: C,61.35; H,9.49; N,8.66.

Methyl 1-methyloxalyl-2-piperidinylacetate (2a): Methyloxalyl chloride (1.57 g, 12.8 mmol) was added dropwise to a solution of the ester 1b (1.968 g, 12.5 mmol) in anhydrous benzene (60 mL) containing dry triethylamine (1.28 g, 12.6 mmol). After the addition was over, stirring was continued for 30 min, and the precipitated white solid was filtered and washed with benzene. The filtrate was evaporated on a rotavapor and the residual oil was chromatographed to produce the N-protected ester 2a (2.80 g, 92%), bp 133-134°C/0.02 mmHg; IR: 1740(ester C=O), 1660 cm^{-1}(amide C=O); ^{1}H NMR(60 MHz): 1.33-2.00(m,6H,C_3-H_2,C_4-H_2,C_5-H_2), 2.47-2.90(m,2H,CH_2CO), 3.17-3.53(m,1H,C_6-H), 3.67(s,3H,OCH_3), 3.87(s,3H, COCOOCH_3), 4.07-5.23(m,2H,C_2-H,C_6-H); EIMS:m/z 243(17,$M^{+\cdot}$), 212(6), 184(8), 170(43), 156(36), 155(26), 142(100), 81(24), 59(37), 41(25). Anal. Calcd. for $C_{11}H_{17}NO_5$: C,54.31; H,7.05; N,5.76. Found: C,54.03; H,7.21; N,5.96.

Methyl 1-ethoxycarbonyl-2-piperidinylacetate (2b): This was prepared (97% yield) by the use of ethyl chloroformate in the procedure described for 2a, distilled as a colourless oil at 102°C/0.15 mmHg; IR: 1745(ester C=O), 1700 cm^{-1} (urethane C=O); ^{1}H NMR(60 MHz): 1.23(t,J=7 Hz,3H,OCH_2CH_3), 1.43-1.97(m,6H,C_3-H_2, C_4-H_2,C_5-H_2), 2.27-3.17(m,3H,CH_2CO,C_6-H), 3.67(s,3H,OCH_3), 3.80-4.37(m containing q at 4.13,J=7 Hz,3H,OCH_2CH_3,C_6-H), 4.43-4.97(m,1H,C_2-H); EIMS:m/z 229(10,$M^{+\cdot}$), 198(5), 157(17), 156(100), 142(11), 128(16), 112(15), 84(31), 56(3), 55(7), 41(2). Anal. Calcd. for $C_{11}H_{19}NO_4$: C,57.62; H,8.35; N,6.11. Found: C,58.06; H,8.12; N,5.78.

Methyl 1-ethoxycarbonyl-6-oxo-2-piperidinylacetate (3b): A solution of the N-protected ester 2b (5.75 g, 25 mmol) in ethyl acetate (90 mL) (previously washed with water) was added to a vigorously stirred mixture of $RuO_2.xH_2O$ (0.575 g) in 10% aqueous $NaIO_4$ (290 mL) at room temperature. After stirring the mixture for 3 h, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were

treated with isopropyl alcohol (5 mL) for 2-3 h to destroy the RuO_4 oxidant. The precipitated black RuO_2 was filtered on a celite pad and the filtrate was washed with water and dried. The solution was stripped of solvent on a rotavapor and the residual oil was purified by column chromatography. The obtained oil was distilled in vacuo to furnish the piperidinone 3b as a colourless liquid (5.68 g, 93%), bp 160°C/0.25 mmHg; IR: 1775, 1740, 1720 cm^{-1}(C=O); ^1H NMR(60 MHz): 1.30(t, J=7 Hz,3H,$OCH_2\underline{CH_3}$), 1.50-2.13(m,4H,C_3-H_2,C_4-H_2), 2.20-2.90(m,4H,C_5-H_2,$\underline{CH_2}CO$), 3.70(s,3H,OCH_3), 4.25(q,J=7 Hz,2H,OCH_2CH_3), 4.47-4.90(m,1H,C_2-H); EIMS:m/z 243(5,$M^{+\cdot}$), 215(5), 212(9), 187(28), 171(9), 170(74), 142(6), 128(13), 126(10), 112(18), 98(100), 70(10), 55(75), 43(18), 42(20), 41(21). Anal. Calcd. for $C_{11}H_{17}NO_5$: C,54.31; H,7.05; N,5.76. Found: C,54.04; H,7.29; N,5.73.

β-Aminopimelic acid (4) hydrochloride: A solution of the piperidinone 3b (5.0 g) in 6N HCl (125 mL) was heated under reflux for 24 h. The solution was concentrated to dryness on a rotavapor to give the hydrochloride of 4 as a white solid in quantitative yield, mp 139-141°C [lit. (6) mp 137-139.5°C]; IR: 1740, 1720 cm^{-1}(C=O); FAB MS:m/z 176(100,MH^+). Though not analytically pure, this was sufficiently pure for further synthetic work. Anal. Calcd. for $C_7H_{14}ClNO_4$: C,39.72; H,6.67; N,6.62. Found: C,38.16; H,6.56; N,6.20.

6-Oxo-2-piperidinylacetic acid (5a): A solution of the hydrochloride of the acid 4 (4.50 g) in dry pyridine (50 mL) was refluxed for 3 h. Pyridine was removed on a rotavapor and the residue was chromatographed to get the piperidinoneacid 5a (2.87 g, 86%). Recrystallization from ethyl acetate provided a crystalline white solid, mp 135-136°C [lit. (6) mp 132-134°C]; IR: 3300(O-H), 3240(N-H), 1720(acid C=O), 1640 cm^{-1}(lactam C=O); ^1H NMR(C^2HCl_3 and a trace of $C^2H_3O^2H$) (60 MHz): 1.27-2.10(m,4H,C_3-H_2,C_4-H_2), 2.13-2.70(m,4H,C_5-H_2,$\underline{CH_2}CO$), 3.47-4.10(m, 1H,C_2-H); EIMS:m/z 157(3,$M^{+\cdot}$), 112(5), 101(39), 98(100), 88(18), 70(17), 56(8), 55(85), 43(17), 42(33).

Methyl 1-methyl-6-oxo-2-piperidinylacetate (5b): A mixture of the piperidinone-acid 5a (2.512 g, 16 mmol) and NaH (2.30 g, 96 mmol) (80% dispersion in oil) (BDH Chemical Co.) in dry N,N-dimethylformamide (50 mL) was stirred under a nitrogen atmosphere for 30 min. Iodomethane (4.55 g, 32 mmol) was added to the white copious mass. The resultant dirty yellow solution was stirred for 1 h at ambient temperature and then for 3 h at 70°C. The reaction mixture was allowed to cool to room temperature, an equal amount of iodomethane was added and left

overnight with stirring. The solution was filtered and the filtrate diluted with water. The aqueous solution was extracted thoroughly with methylene chloride. The combined organic extracts were washed with brine and dried. The solvent was evaporated on a rotavapor and the residue was extracted with petroleum ether (bp 35-60°C). The residual solid was characterized as the monomethylated product 5c (vide infra). The combined petroleum ether washings were evaporated and the resultant oil was distilled in vacuo to give the piperidinoneester 5b as a pale yellow liquid (2.16 g, 73%), bp 65-67°C/0.01 mmHg [lit. (7) bp 100-102°C/ 0.2 mmHg]; IR: 1735(ester C=O), 1640 cm^{-1}(lactam C=O); ^{1}H NMR(60 MHz): 1.47-2.10 (m,4H,C_3-H_2,C_4-H_2), 2.17-2.73(m,4H,C_5-H_2,CH_2CO), 2.90(s,3H,NCH_3), 3.50-4.07 (m containing OCH_3 spike at 3.70,4H,OCH_3,C_2-H); EIMS:m/z 185(11,$M^{+\cdot}$), 157(11), 129(10), 112(100), 84(7), 70(2), 56(2), 55(18), 43(1), 42(7).

Methyl 6-oxo-2-piperidinylacetate (5c): This was obtained from the above reaction as a cream coloured solid from ether, mp 94-95°C; IR: 3200(N-H), 1735(ester C=O), 1680 cm^{-1}(lactam C=O); ^{1}H NMR(60 MHz): 1.23-2.13(m,4H,C_3-H_2, C_4-H_2), 2.17-2.73(m,4H,C_5-H_2,CH_2CO), 3.50-4.07(m containing OCH_3 spike at 3.70, 4H,OCH_3,C_2-H), 6.77(br s,1H,NH,D_2O exchangeable); EIMS:m/z 171(16,$M^{+\cdot}$), 143(20), 115(40), 112(6), 98(100), 70(9), 56(5), 55(56), 43(9), 42(13). Anal. Calcd. for $C_8H_{13}NO_3$: C,56.13; H,7.65; N,8.18. Found: C,55.94; H,8.01; N,8.06.

2-(2-Hydroxyethyl)-1-methyl-6-piperidinone (6a): To a stirred and refluxed suspension of the piperidinoneester 5b (1.48 g, 8 mmol) and $NaBH_4$ (0.91 g, 24 mmol) in anhydrous THF (30 mL), methanol (6.5 mL) was added dropwise over a 1 h period. The resultant turbid solution was then refluxed for 5 h. After allowing it to cool to room temperature, the reaction mixture was decomposed with cold water and concentrated to dryness on a rotavapor. The residue was extracted with methylene chloride and the combined organic extracts were dried and evaporated on a rotavapor. The oil was purified using column chromatography to give a pure colourless oil (0.955 g, 76%), which solidified on refrigeration to afford 6a as a white solid, mp 45-46°C [lit. (7) bp 160°C/0.3 mmHg]; IR: 3400(O-H), 1615 cm^{-1}(lactam C=O); ^{1}H NMR(60 MHz): 1.33-2.10(m,6H,C_3-H_2,C_4-H_2,CH_2CH_2OH), 2.13-2.53(m,2H,C_5-H_2), 2.90(s,3H,NCH_3), 3.20-3.93(m,3H,CH_2OH,C_2-H), 4.20-4.63(m, 1H,OH,D_2O exchangeable); EIMS:m/z 157(4,$M^{+\cdot}$), 126(2), 112(100), 84(6), 70(3), 56(4), 55(27), 43(3), 42(14). Anal. Calcd. for $C_8H_{15}NO_2$: C,61.12; H,9.62; N,8.91. Found: C,61.14; H,9.23; N,8.58.

2-(2-Hydroxyethyl)-1-methylpiperidine (6b): (i) From the piperidinonealcohol 6a. A solution of the piperidinonealcohol 6a (0.205 g, 1.3 mmol) in dry THF (3 mL) was added slowly to a stirred suspension of LAH (0.10 g, 2.6 mmol) in dry ether (15 mL) at 0°C. After the addition was complete , the reaction mixture was refluxed for 4 h. Excess LAH was decomposed cautiously with moist ether, followed by the addition of 20% aqueous NaOH. The solvents were decanted off and the residual white cake was extracted with ether. The combined organic solvents were evaporated and the oil was taken up in ether, washed with brine and dried. The solvent was stripped off on a rotavapor to leave the alcohol 6b, which distilled in vacuo as a colourless liquid (0.18 g, 96%), bp 62-63°C/0.6 mmHg [lit. (11) bp 80°C/2 mmHg]; IR: 3300 cm^{-1}(O-H); ^{1}H NMR(60 MHz): 1.33-2.30(m, 10H,C_3-H_2,C_4-H_2,C_5-H_2,C_6-H_2,CH_2CH_2OH), 2.37(s,3H,NCH_3), 2.83 (m,1H,C_2-H), 3.83(m, 2H,CH_2OH), 4.40(br s,1H,OH,D_2O exchangeable); EIMS:m/z 143(4,$M^{+\cdot}$), 142(3), 141(5), 140(7), 112(4), 98(100), 84(9), 70(10), 42(6), 41(3).

(ii) - From the piperidinoneester 5b. To a stirred suspension of LAH (0.19 g, 5 mmol) in dry ether (40 mL) at 0°C, a solution of the piperidinoneester 5b (0.37 g, 2 mmol) in ether (5 mL) was added slowly. The resultant reaction mixture was refluxed for 7 h after which it was worked up as usual to furnish the alcohol 6b (0.26 g, 91%)(identical TLC, co-TLC, and IR, ^{1}H NMR and EIMS spectra with the above sample).

(iii) - From the piperidinone 3b. A solution of the piperidinone 3b (0.243 g, 1 mmol) in dry ether (5 mL) was added to the stirred suspension of LAH (0.152 g, 4 mmol) in dry ether (25 mL) at 0°C. The reaction mixture was refluxed for 24 h and usual workup provided the alcohol 6b (0.12 g, 84%)(identical TLC, co-TLC, and IR, ^{1}H NMR and EIMS spectra with the above sample).

2-(2-Hydroxyethyl)-1-methyl[6,6-$^2H_2$]piperidine (6c): This was prepared by use of LAD in the method (i) from the piperidinonealcohol 6a, TLC and co-TLC as for 6b; IR: 3300 cm^{-1}(O-H); ^{1}H NMR(60 MHz): 1.00-2.23(m,9H,C_2-H,C_3-H_2,C_4-H_2,C_5-H_2, CH_2CH_2OH), 2.30(s,3H,NCH_3), 3.73(m,2H,CH_2OH), 5.20(br s,1H,OH).

2-(2-Hydroxy[1,1-$^2H_2$]ethyl)-1-methyl[6,6-$^2H_2$]piperidine (6d): This was prepared from the piperidinoneester 5b and LAD using the procedure (ii) described for 6b, TLC and co-TLC as for 6b; IR: 3300 cm^{-1}(O-H); ^{1}H NMR(60 MHz): 1.10-2.23(m,9H, C_2-H,C_3-H_2,C_4-H_2,C_5-H_2,$CH_2C^2H_2OH$), 2.33(s,3H,NCH_3), 4.80(br s,1H,OH); EIMS:m/z 147(1,$M^{+\cdot}$), 146(1), 145(0.4), 144(0.2), 100(100), 72(23), 43(10), 42(18).

2-(2-Chloroethyl)-1-methylpiperidine (7a): Thionyl chloride (3.0 g, 25 mmol) was added dropwise to a stirred ice-cooled solution of the alcohol 6b (2.5 g, 17 mmol) in dry chloroform (15 mL). After the addition was complete, the solution was refluxed on a steam bath for 3 h. The solvent and excess thionyl chloride were removed on a rotavapor and the residual solid was dissolved in 25% aqueous HCl (125 mL) and treated with Norit. The filtered solution was evaporated to dryness on a rotavapor and the solid so obtained recrystallized from acetone as white crystals of 7a hydrochloride (3.01 g, 87%), mp 131-132°C [lit. (11) mp 132-133°C]; ^{1}H NMR(free base)(60 MHz): 1.17-2.23(m,10H,C_3-H_2,C_4-H_2,C_5-H_2, C_6-H_2,CH_2CH_2Cl), 2.33(s,3H,NCH_3), 2.83(m,1H,C_2-H), 3.67(m,2H,CH_2Cl); EIMS:m/z 163/161(1/3,$M^{+\cdot}$), 112(0.4), 98(100), 84(2), 70(11), 56(1), 55(3), 43(12), 42(10), 41(4).

2-(2-Chloroethyl)-1-methyl[6,6-$^2H_2$]piperidine (7b): This was prepared from the alcohol 6c using the method described for 7a, mp and admixture mp with the non-deuterated hydrochloride salt as for 7a; ^{1}H NMR(free base)(60 MHz): 1.00-2.20(m, 9H,C_2-H,C_3-H_2,C_4-H_2,C_5-H_2,CH_2CH_2Cl), 2.30(s,3H,NCH_3), 3.63(m,2H,CH_2Cl); EIMS: m/z 165/163(0.4/1.3,$M^{+\cdot}$), 100(100), 86(1), 72(9), 56(1), 55(2), 43(3), 42(10).

2-(2-Chloro[1,1-$^2H_2$]ethyl)-1-methyl[6,6-$^2H_2$]piperidine (7c): This was prepared from the alcohol 6d using the method described for 7a, mp and admixture mp with the nondeuterated hydrochloride salt as for 7a; ^{1}H NMR(free base)(300.13 MHz): 1.25-2.09(m,9H,C_2-H,C_3-H_2,C_4-H_2,C_5-H_2,$CH_2C^2H_2Cl$), 2.26(s,3H,NCH_3); EIMS:m/z 167/165(0.6/1.9,$M^{+\cdot}$), 100(100), 86(1), 72(17), 56(2), 55(3), 43(7), 42(10).

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 dry toluene (10 mL) (dried over molecular sieves Type 5A) was refluxed for 5 h in an atmosphere of nitrogen in the absence of direct intense light. The hydrochloride of 7a (0.435 g, 2.2 mmol) was then introduced slowly in small portions over a period of 1 h while continuing the refluxing. The resultant almost colourless solution was refluxed for an additional 3 h. The cooled reaction mixture was washed with water and then extracted with dilute HCl. The combined acid extracts were basified with NaOH and the liberated base was extracted into methylene chloride. The combined organic extracts were washed with water, dried and evaporated on a rotavapor. The resultant oily residue was chromatographed 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(300.13 MHz): 1.17-2.15(m,10H,C_3-H_2,C_4-H_2,C_5-H_2, C_6-H_2,$Ar_2NCH_2CH_2$), 2.21(s,3H,NCH_3), 2.45(s,3H,SCH_3), 2.83(m,1H,C_2-H), 3.87(m,2H, Ar_2NCH_2), 6.80-7.14(m,7H,ArH); ^{13}C NMR: 145.61, 144.88, 137.45, 127.44, 127.34, 127.11, 125.18, 122.45, 122.10, 120.66, 115.60, 114.48, 62.01, 56.82, 43.85, 43.09, 30.82, 29.97, 25.66, 24.14, 16.38; EIMS:m/z 370(14,$M^{+\cdot}$), 258(3), 245(2), 244(3), 185(3), 126(9), 112(1), 98(100), 70(11), 42(7), 41(2). The oil was treated with ethereal HCl and the solid so obtained was recrystallized from acetone as white crystals of 9a hydrochloride, mp 157-159°C [lit. (12) mp 158-160°C], and admixture with the authentic commercial sample (mp 156-158°C) did not show any depression.

10-[2-(1-Methyl-2-[6,6-$^{2}H_2$]piperidinyl)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 hydrochloride salt as for 9a; ^{1}H NMR (300.13 MHz): 1.21-2.10(m,9H,C_2-H,C_3-H_2,C_4-H_2,C_5-H_2,$Ar_2NCH_2CH_2$), 2.21(s,3H, NCH_3), 2.45(s,3H,SCH_3), 3.90(m,2H,Ar_2NCH_2), 6.80-7.35(m,7H,ArH); ^{13}C NMR: 145.72, 144.95, 137.55, 127.54, 127.45, 127.21, 125.35, 122.58, 122.29, 120.82, 115.71, 114.61, 62.10, 56.03(q,J=20 Hz), 43.93, 42.97, 30.73, 29.90, 25.31, 24.02, 16.47; EIMS:m/z 372(13,$M^{+\cdot}$), 258(3), 245(3), 244(3), 185(3), 128(9), 114(1), 100(100), 72(8), 43(6), 42(6).

10-[2-(1-Methyl-2-[6,6-$^{2}H_2$]piperidinyl)[1,1-$^{2}H_2$]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(300.13 MHz): 1.20-2.20(m,9H,C_2-H,C_3-H_2,C_4-H_2,C_5-H_2,$Ar_2NC^{2}H_2CH_2$), 2.23(s,3H,NCH_3), 2.45(s,3H,SCH_3), 6.79-7.25(m,7H,ArH); ^{13}C NMR: 145.68, 144.89, 137.60, 127.56, 127.47, 127.24, 125.33, 122.61, 122.26, 120.84, 115.70, 114.58, 62.12, 56.01(q,J=20 Hz), 43.29(q,J=20 Hz), 42.81, 30.62, 29.60, 25.18, 23.94, 16.47; EIMS:m/z 374(15,$M^{+\cdot}$), 260(3), 245(2), 244(2), 185(2), 130(10), 114(2), 100(100), 72(7), 43(4), 42(5).

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