SYNTHESIS OF DEUTERIUM LABELLED PERPHENAZINE

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SUMMARY

Procedures for the preparation of perphenazine-d_2, -d_4, and -d_6, and *N*-deshydroxyethylperphenazine-d_4 and -d_6 are described. Deuterium was introduced in the propylpiperazine side chain by treatment of the appropriate ester or imide with lithium aluminum deuteride. The γ-carbon of the propyl group was labelled with two deuterium atoms by reduction of 2-chloro-10-(2-methoxycarbonylethyl)-10*H*-phenothiazine, while four deuterium atoms were incorporated into the piperazine ring by reduction of 2-chloro-10-[3-(3,5-dioxo-1-piperazinyl)-propyl]-10*H*-phenothiazine.

Key Words: Perphenazine, deuterium labelling.

INTRODUCTION

Perphenazine (Scheme 1, 1a), a piperazine type phenothiazine, is generally administered in low oral or intramuscular doses as an antipsychotic or anti-emetic agent. The ensuing (low ng) plasma levels, as well as the reputed notorious instability and adsorptive loss in all stages of handling for analysis of this group of drugs, make the quantitation of perphenazine in the plasma of patients under treatment difficult. A radioimmunoassay procedure which is capable of quantitating 0.25 ng of perphenazine per millilitre of plasma, using a 200 µl plasma sample, has been reported from the authors' laboratories (1). In order to verify the specificity of this sensitive biological procedure, a specific and sensitive chemical method such as gas chromatography-mass spectrometry (GLC-MS) is required. A stable isotope analogue of perphenazine was needed as a true internal standard in order to obtain the required sensitivity on GLC-MS. In addition further stable isotopically labelled analogues of perphenazine were

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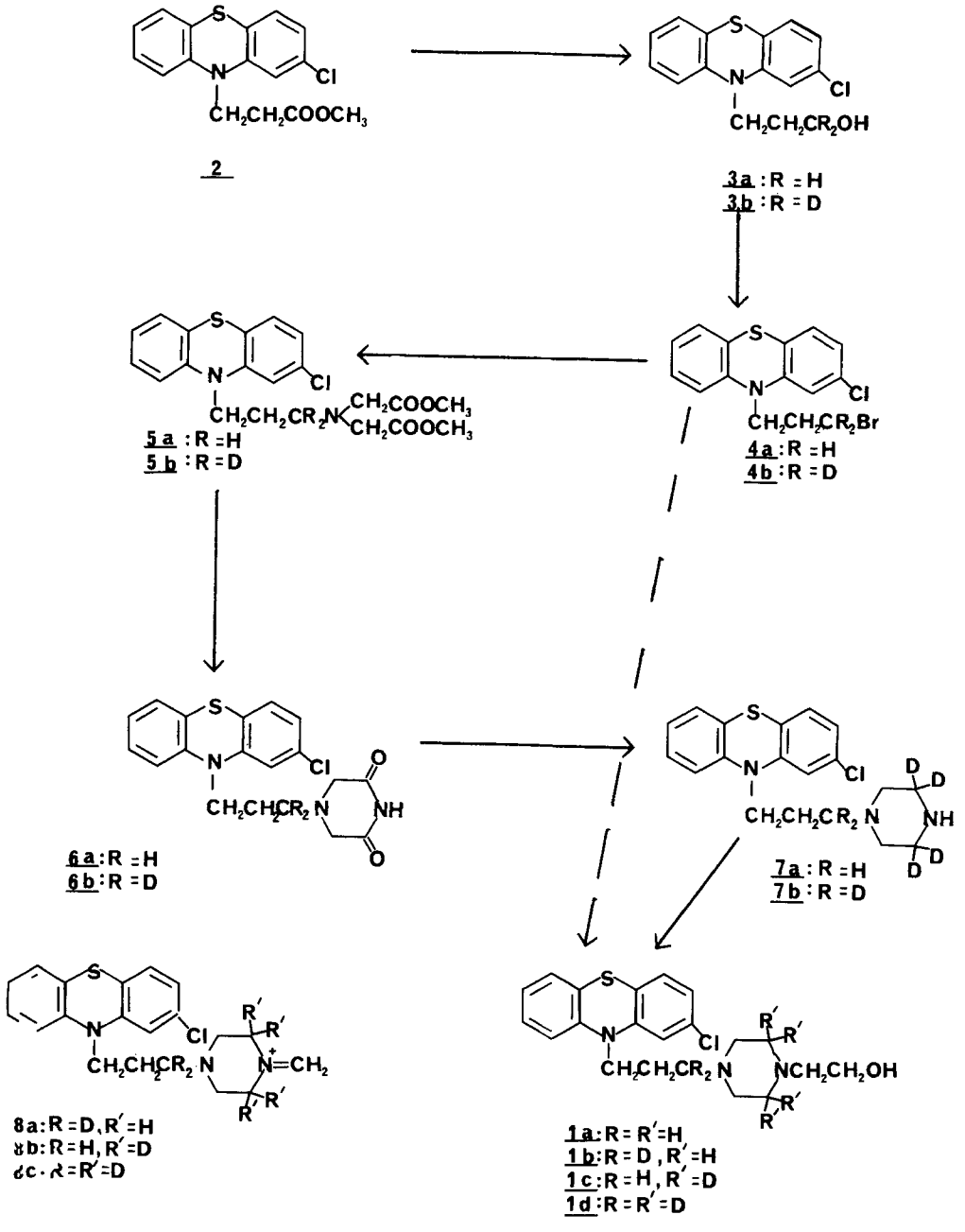
required for administration to animals or humans by one or two routes so as to allow reliable pharmacokinetics, including absolute and relative bioavailability, to be determined with the analysis of plasma concentrations by GLC-MS using a selected ion monitoring technique. Such studies will enable definitive pharmacokinetics of perphenazine to be obtained with far fewer administrations, using far fewer individuals, than would otherwise be possible. This paper describes the synthesis of perphenazine with two, four, and six deuterium atoms in the propylpiperazine side chain. This site of label was chosen since it is generally not lost metabolically and allows adequate variation in the number of labelled atoms.

DISCUSSION

The syntheses of *N*-10 side chain deuterium labelled piperazine type phenothiazines have been previously reported from these laboratories. Thus prochlorperazine (2) and trifluoperazine (3), *N*-methylpiperazine type phenothiazines, were labelled with two, four, and six deuterium atoms in the propylpiperazine side chain. Two deuterium atoms were incorporated in the propyl chain by lithium aluminum deuteride reduction of a carbonyl group α to the piperazine ring. An analogous synthesis of dideuterated N-hydroxyethylpiperazine type phenothiazines, such as perphenazine, would require protection of the alcoholic function for such a reduction step. Thus perphenazine-d_2 was synthesized by an alternate approach (Scheme 1). The key step in this sequence (2→3b→4b→1b) was the preparation of 3-[10-(2-chlorophenothiazinyl)]propan-1-ol-d_2 (3b) by lithium aluminum deuteride reduction of the methyl propionate (2), a reaction previously reported for the unlabelled compound (3a) where the propionic acid derivative of 2 was reduced (4). The final two steps to perphenazine-d_2 (3b→4b→1b) proceeded smoothly with involvement of the bromopropyl compound (4b), synthesized by bromination


2
3a : R = H
3b : R = D
4a : R = H
4b : R = D
5a : R = H
5b : R = D
6a : R = H
6b : R = D
7a : R = H
7b : R = D
8a: R = D, R′ = H
8b: R = H, R′ = D
8c: R = R′ = D
1a: R = R′ = H
1b: R = D, R′ = H
1c: R = H, R′ = D
1d: R = R′ = D

Scheme 1

of the alcohol with triphenylphosphine and *N*-bromosuccinimide (5), rather than the chloropropyl analogue of 4 invariably used in phenothiazine syntheses of this type.

For the previously reported syntheses to prochlorperazine-d_4 (2) and trifluoperazine-d_4 (3) the key intermediate involved was 1-methyl(3,3,5,5,-$^2H_4$)-piperazine, prepared by lithium aluminum deuteride reduction of 1-methyl-3,5-piperazinedione. An analogous synthesis to perphenazine-d_4 would require an appropriately labelled 1-(2-hydroxyethyl)piperazine. However, all attempts to obtain the desirably labelled piperazine failed. Thus, for example, the previously reported 1-(2-hydroxyethyl)-3,5-piperazinedione (6) and 1-(2-hydroxyethyl)-2,3-piperazinedione (7) appeared as suitable precursors to the desired labelled piperazine. However, the former precursor could not be isolated in a pure form, while the latter gave ring opened products on lithium aluminum hydride reduction, as previously reported for a similar reduction of 2,3-piperazinedione (8). Thus a route to perphenazine-d_4 was developed where the piperazine ring was built stepwise on to the propyl side chain (4b→7a→1c). This route started with 2-chloro-10(3-bromopropyl)-10*H*-phenothiazine (4a), rather than its reputedly more readily accessible 3-chloropropyl analogue. The latter is reported to be synthesized from treatment of 2-chlorophenothiazine with 1-bromo-3-chloropropane and a strong base catalyst (9,10). However, in our hands, such syntheses, as with the use of $NH_3/NaNH_2$ (9), NaOH in DMF (10), and NaH in DMSO (11) gave the dechlorinated product, 10-(3-chloropropyl)-10*H*-phenothiazine, as well as the desired 2-chloro-10-(3-chloropropyl)-10*H*-phenothiazine; compounds which were found to be difficult to separate. Thus the bromopropyl compound (4a), prepared as discussed above (2→3a→4a), was treated with methyl iminodiacetate (4a→5a), while subsequent alkaline hydrolysis followed by urea fusion (5a→6a), gave the key imide intermediate (6a).

Reduction with lithium aluminum deuteride (6a→7a) afforded the d_4 labelled N-desalkyl metabolite of perphenazine and prochlorperazine (7a). Finally alkylation of 7a gave greater yields of the desired perphenazine-d_4 (1c) with 2-bromoethanol as reagent rather than ethylene oxide.

This new synthetic route to perphenazine was subsequently utilized in order to synthesize perphenazine-d_6 (4b→7b→1d), as well as the d_6 labelled *N*-desalkyl metabolite of perphenazine and prochlorperazine (7b), starting from the 2-chloro-10-(3-bromopropyl)-10*H*-phenothiazine-d_2 (4b) compound previously discussed.

The isotopic purity of the labelled purified products was determined by GLC-MS of the TMS derivative of the compound, where a single ion formed from the loss of CH_2OTMS from the parent ion (Scheme 1, 8a-8c) was monitored. The $(^{35}Cl)\ ^2Ho/^2Hn$ ratios for these ions were determined to be 5.57, 1.98, and 0.43% for the di-(n=2), tetra-(n=4), and hexa-(n=6) deuterated perphenazine, respectively. This purity is sufficient for their use in pharmacokinetic studies as well as true internal standards in GLC-MS analysis. These studies will be reported elsewhere.

EXPERIMENTAL

The melting points were determined on an electrothermal melting point apparatus and are uncorrected. All thin-layer chromatography (TLC) was carried out on pre-coated fluorescent sheets where spots were observed under ultraviolet light. PMR spectra were determined on a Varian T-60 instrument; chemical shifts are expressed in δ units (part per million) relative to TMS. Low resolution electron impact mass spectra (EIMS) were routinely recorded on a VG Micromass MM16F instrument at 70 eV equipped with a VG 2025 data system; relative intensity is noted in parentheses after each major fragment.

Interface of this system with a Hewlett Packard 5710A gas chromatograph gave the GLC-mass spectrometry system: the chromatographic column was a 2m glass tube (2mm i.d.) packed with 3% OV-1 on Gas Chrom Q, 100-120 mesh, the ionizing voltage was 70 eV, and the source temperature 180°. Microanalyses for samples dried over phosphorous pentoxide at 60° under reduced pressure, were performed by Mr. R.E. Teed, Department of Chemistry and Chemical Engineering.

2-Chloro-10-(3-hydroxypropyl)-10*H*-phenothiazine (3a). A solution of 6.396 g (20 mmol) of 2-chloro-10-(2-methoxycarbonylethyl)-10*H*-phenothiazine (2) [m.p. 73-74°C (lit. (12) m.p. 71.5-72.5°C) TLC:Rf (90 C_6H_6:10 $C_2H_5OCOCH_3$) 0.74] prepared as reported (12), in dry ether (40 ml) was added dropwise over 30 min. to a magnetically stirred suspension under dry nitrogen of lithium aluminum hydride (0.759 g, 20 mmol) in dry ether (40 ml) at 0°C. After stirring for an additional 2 hr. at room temperature moist ether (40 ml) and 10% HCl (40 ml) were successively added dropwise with stirring to the reaction mixture maintained at 0°C. The organic layer was separated and the aqueous layer was washed with ether (40 ml). The combined ether fractions were dried ($MgSO_4$), and evaporated under reduced pressure to give a pale yellow liquid which solidified on standing. Recrystallization from benzene-hexane afforded the alcohol (3a) (4.085 g, 68%), m.p. 118-119°C (lit. (4) m.p. 124-125°C) as pale white crystals; TLC:Rf (90 C_6H_6:10 $C_2H_5OCOCH_3$) 0.40.

2-Chloro-10-[3-hydroxy(3,3-$^2H_2$)propyl]-10*H*-phenothiazine (3b). This was prepared (70% yield) by the lithium aluminum deuteride reduction of 2 using the method described for 3a: m.p. and TLC as for 3a.

2-Chloro-10-(3-bromopropyl)-10*H*-phenothiazine (4a). To a stirred solution of the propanol (3a) (2.918 g, 10 mmol) and triphenylphosphine (3.934 g, 15 mmol) in dry acetonitrile (30 ml) was added dropwise over 30 min. a solution of *N*-bromosuccinimide (2.670 g, 15 mmol) in dry acetonitrile (20 ml). The re-

action mixture was stirred at room temperature for a further 1 hr., the solvent removed under reduced pressure, and the residue partitioned between benzene (50 ml) and water (50 ml). The benzene layer was washed several times with water and subsequently dried ($MgSO_4$). The residue left after removal of the benzene was digested with *n*-hexane (100 ml), cooled, and the precipitated triphenylphosphine oxide was filtered and washed with warm *n*-hexane. The filtrate on passing through a neutral alumina column with hexane-benzene (70:30) gave 4a as a pale yellow viscous oil (3.476 g, 98%) (lit. (13) oil reported for tritiated compound, no analysis or spectra given); TLC:Rf (90 C_6H_6:10 $C_2H_5OCOCH_3$) 0.78; PMR($CDCl_3$): δ 2.00-2.50(m,2H,propyl central CH_2), 3.44(t,2H,CH_2-Br,J=6Hz), 3.97(t,2H,CH_2-phenothiazine,J=6Hz), 6.67-7.34(m,7H, aromatic H); EIMS: 353/355/357($M^{+\cdot}$)(58/73/25), 273/275(18/6), 246/248(69/28), 233/235(24/10), 232/234(100/40), 214/216(28/9), 196(14). Anal. Calcd. for $C_{15}H_{13}BrClNS$: C, 50.79; H, 3.69; N, 3.95. Found: C,50.42; H, 3.59; N, 4.09.

2-Chloro-10-[3-bromo(3,3-$^2H_2$)propyl]-10*H*-phenothiazine (4b). This was prepared (96% yield) from 3b by the method described for 4a: m.p. and TLC as for 4a; PMR($CDCl_3$): δ 2.22(t,2H,CH_2-CD_2,J=6Hz), 3.96(t,2H,CH_2-phenothiazine), 6.62-7.23(m,7H,aromatic H).

2-Chloro-10-[[3-[4-(2-hydroxyethyl)-1-piperazinyl] (3,3-$^2H_2$)propyl]]-10*H*-phenothiazine dihydrochloride (1b). A mixture of 4b (1.070 g, 3 mmol) and 2-hydroxyethylpiperazine (0.781 g, 6 mmol) in dry methyl ethyl ketone (30 ml) was refluxed for 4 hr. The solvent was removed under vacuum and the residue was digested with 10% HCl (30 ml). The acidic solution was washed with diethyl ether (3 x 15 ml) and the combined ether wash was extracted with 10% HCl (15 ml). The combined acid fractions were basified (Na_2CO_3) and extracted with ether (5 x 15 ml). The combined ether extracts were washed with water, dried (Na_2SO_2), filtered, and evaporated under reduced pressure to yield a pale

yellow oil, which was treated with acetonitrile (10 ml) and ethereal HCl. Recrystallization of the precipitated solid from absolute EtOH gave perphenazine-d_2 dihydrochloride (1b) (0.963 g, 67%), m.p. 218-219° (lit. (15) unlabelled m.p. 222°C). Mixed melting points with authentic unlabelled samples (1a), prepared by the same route with lithium aluminum hydride or from a commercial source, were not depressed; TLC:Rf (100 CH_3COCH_3:1 NH_3) 0.47; PMR(free base, $CDCl_3$): δ 1.71-2.04(m,2H,propyl central CH_2), 2.20-2.65(m,11H,CH_2-piperazine,piperazine CH_2 and O-H), 3.50(t,2H,CH_2-O,J=5Hz), 3.81(t,2H,CH_2-phenothiazine,J=6.5Hz), 6.64-7.24(m,7H,aromatic H); EIMS: 405/407($M^{+\cdot}$)(48/20), 374/376(29/12), 274/276(36/8), 246/248(100/38), 233/235(38/20), 232/234(41/25), 173(29), 159(28), 145(69), 115(41), 100(43).

2-Chloro-10-[3-(*N*,*N*-dimethoxycarbonylmethyl)aminopropyl]-10*H*-phenothiazine (5a).

A mixture of 4a (4.349 g, 10 mmol), iminodiacetic acid dimethyl ester (15) (4.029 g, 25 mmol), and sodium iodide (1.499 g, 10 mmol) was refluxed in dry methyl ethyl ketone (25 ml) for 24 hr. The solvent was removed under vacuum to leave an oily residue, which was dissolved in 15% HCl (20 ml). The acidic solution was washed with diethyl ether (2 x 10 ml) and then neutralized with Na_2CO_3. The oil that separated was extracted into diethyl ether (3 x 15 ml), and the combined ethereal extracts were washed with water (2 x 5 ml), and dried ($MgSO_4$). Removal of the ether afforded an oil, which was passed through a silica gel column eluting with ether. Evaporation of the ether afforded 4a as a colourless viscous oil (4.045 g, 93%); TLC:Rf (90 C_6H_6:10 $C_2H_5OCOCH_3$) 0.41; PMR($CDCl_3$): δ 1.63-2.10(m,2H,propyl central CH_2), 2.80(t,2H,CH_2-side chain N,J=6.5Hz), 3.44(s,4H,CH_2-CO), 3.59(s,6H,CH_3-O), 3.92(t,2H,CH_2-phenothiazine,J=6Hz), 6.63-7.18(m,7H,aromatic H); EIMS: 434/436($M^{+\cdot}$)(6/2), 233/235(9/3), 186(8), 175(10), 174(32), 146(12), 116(100), 102(15). Anal. Calcd. for $C_{21}H_{23}ClN_2O_4S$: C, 57.99; H, 5.33; N, 6.44. Found: C, 57.89; H, 5.17; N, 6.41.

2-Chloro-10-[3-(*N*,*N*-dimethoxycarbonylmethyl)amino(3,3-$^2H_2$)propyl]-10*H*-phenothiazine (5b). This was prepared (90% yield) from 4b by the method described for 5a: m.p. and TLC as for 5a; PMR($CDCl_3$): δ 1.83(t,2H,CH_2-CD_2,J=6.5Hz), 3.40(s,4H,CH_2-CO), 3.57(s,6H,CH_3-O), 3.85(t,2H,CH_2-phenothiazine,J=6.5Hz), 6.56-7.21(m,7H,aromatic H).

2-Chloro-10-[3-(3,5-dioxo-1-piperazinyl)propyl]-10*H*-phenothiazine (6a). The ester (5a) (2.175 g, 5 mmol) was hydrolyzed by treatment with aqueous MeOH (15 ml MeOH and 15 ml H_2O) containing NaOH (0.8 g, 20 mmol), heated under reflux on a steam bath for 1 hr. The cooled solution was diluted with water (25 ml) and the pH adjusted to 3.0. The precipitated product was filtered and washed with water to afford the acid intermediate (1.770 g, 87%), m.p. 128-129°. The finely powdered acid (1.221 g, 3 mmol) and urea (0.198 g, 3.3 mmol) were mixed and heated to 175°C on an oil bath, and held at this temperature for 2 hr. with stirring. The mixture was cooled and the solidified product was dissolved in boiling EtOH, treated with activated charcoal and filtered. The solid which separated on cooling was recrystallized from EtOH to yield the desired imide (6a) (0.791 g, 68%), m.p. 144-145°C as pale white crystals; TLC:Rf (90 C_6H_6:10 MeOH) 0.88; PMR(DMSO-d_6): δ 1.57-1.94(m, 2H,propyl central CH_2), 3.00-3.38(m,6H,CH_2-CO and CH_2-piperazine), 3.87(t, 2H,CH_2-phenothiazine,J=6.5Hz), 6.69-7.14(m,7H,aromatic H), 9.22(s,1H,N-H); EIMS: 387/389($M^{+\cdot}$)(100/38), 272/274(13/6), 246/248(33/12), 233/235(55/21), 232/234(73/33), 214/216(22/7), 155(63), 127(48). Anal. Calcd. for $C_{19}H_{18}ClN_3O_2S$; C, 58.83; H, 4.68; N, 10.83. Found: C, 58.82; H, 4.82; N, 10.65.

2-Chloro-10-[3-(3,5-dioxo-1-piperazinyl)(3,3-$^2H_2$)propyl]-10*H*-phenothiazine (6b). This was prepared (66% yield) from the labelled ester (5b) by the method described for 6a: m.p. and TLC as for 6a; PMR(DMSO-d_6): δ 2.91(t,2H,CH_2-CD_2,

J=6Hz), 3.24(s,4H,CH_2-CO), 3.87(t,2H,CH_2-phenothiazine,J=6Hz), 6.69-7.20(m, 7H,aromatic H), 9.25(s,1H,N-H); EIMS: 389/391($M^{+\cdot}$)(97/43), 274/276(20/9), 246/248(38/17), 233/235(60/27), 232/234(100/73), 214/216(32/10), 157(94), 129(61).

2-Chloro-10-[[3-[1-(3,3,5,5-$^2H_4$)piperazinyl]propyl]]-10*H*-phenothiazine dimaleate (7a). To a stirred suspension of lithium aluminum deuteride (0.504 g, 12 mmol) in dry THF (10 ml) at 0°C under nitrogen was added dropwise over 30 min. a solution of the imide (6a) (1.164 g, 3 mmol) in dry THF (10 ml). After 2 hr. under reflux, moist ether (10 ml) and water (2 ml) were successively slowly added dropwise with stirring at 0°C. The precipitated inorganic material was filtered off and extracted with ether in a Soxhlet apparatus. The combined ether solution was dried (Na_2SO_4), filtered, and evaporated to dryness. The yellow oily residue was dissolved in acetone (10 ml) and treated with maleic acid (0.813 g, 7 mmol) in acetone (5 ml). The solid which separated was recrystallized from absolute EtOH to yield *N*-deshydroxyethylperphenazine-d_4 dimaleate (7a) (1.252 g, 70%), m.p. 162-163°C (lit. (16) m.p. 156-158°C). Mixed melting points with authentic unlabelled samples, prepared by the same route with lithium aluminum hydride or from a commercial source, were not depressed; TLC:Rf (80 C_6H_6:20MeOH) 0.70; PMR(free base $CDCl_3$): δ 1.87-2.04(m, 3H,propyl central CH_2 and N-H), 2.09-2.60(m,6H,CH_2-piperazine and piperazine CH_2), 3.87(t,2H,CH_2-phenothiazine,J=6.5Hz), 6.63-7.22(m,7H,aromatic H); EIMS: 363/365($M^{+\cdot}$)(100/43), 331/333(6/2), 273/275(12/4), 272/274(14/12), 246/248 (10/7), 233/235(17/6), 232/234(15/8), 214/216(11/4), 131(18), 103(43).

2-Chloro-10-[[3-[1-(3,3,5,5-$^2H_4$)piperazinyl](3,3-$^2H_2$)propyl]]-10*H*-phenothiazine dimaleate (7b). *N*-Deshydroxyethylfluphenazine-d_6 (7b) was prepared (68% yield) from 6b by the method described above for 7a: m.p. and TLC as for 7a; PMR(free base, $CDCl_3$): δ 1.80-2.07(m,3H,propyl central CH_2 and N-H),

2.33(s,4H,piperazine $C\underline{H}_2$), 3.86(t,2H,$C\underline{H}_2$-phenothiazine,$\underline{J}$=6.5Hz), 6.59-7.29(m, 7H,aromatic $\underline{H}$); EIMS: 365/367($M^{+\cdot}$)(53/21), 332/334(6/2), 331/333(4/4), 274/276(13/6), 259/261(13/6), 233/235(24/9), 232/234(17/12), 198(13), 133(43), 105(100).

2-Chloro-10-[[3-[4-(2-hydroxyethyl)-1-(3,3,5,5-$^2H_4$)piperazinyl]propyl]]-10*H*-phenothiazine dimaleate (1c). A mixture of *N*-deshydroxyethylperphenazine-d_4 (7a) (1.080 g of free base, 3 mmol), 2-bromoethanol (0.412 g, 3.3 mmol), and potassium carbonate (0.415 g, 3 mmol) in dry methyl ethyl ketone (30 ml) was refluxed under dry nitrogen for 3 hr. The solvent was removed under reduced pressure and the residue dissolved in 15% HCl (20 ml). This acidic solution was washed with ether (2 x 10 ml), basified (Na_2CO_3), and extracted with ether (4 x 15 ml). The ether layers were combined, washed with water, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. The oily residue was dissolved in acetone (10 ml), treated with maleic acid (0.731 g, 6.3 mmol) in acetone (10 ml), and the solid which separated was recrystallized from absolute EtOH to afford perphenazine-d_4 dimaleate (1c) (1.145 g, 60%), m.p. 170-171°C (lit. (14) unlabelled m.p. 177°C). Mixed melting points with authentic undeuterated samples, prepared by the same route with unlabelled reagents or from a commercial source, were not depressed; TLC:Rf (100 CH_3COCH_3:1 NH_3) 0.72; PMR(free base, $CDCl_3$): δ 1.76-2.04(m,2H,propyl central $C\underline{H}_2$), 2.12-2.61(m,9H,$C\underline{H}_2$-piperazine,piperazine $C\underline{H}_2$,and O-$\underline{H}$), 3.52(t,2H,$C\underline{H}_2$-O, $\underline{J}$=5Hz), 3.85(t,2H,$C\underline{H}_2$-phenothiazine,$\underline{J}$=6.5Hz), 6.61-7.18(m,7H,aromatic $\underline{H}$); EIMS: 407/409($M^{+\cdot}$)(32/15), 376/378(13/6), 247/249(19/8), 246/248(100/31), 232/234(20/8), 214/216(18/6), 175(20), 161(19), 147(57), 117(32), 103(22).

2-Chloro-10-[[3-[4-(2-hydroxyethyl)-1-(3,3,5,5-$^2H_4$)piperazinyl](3,3-$^2H_2$)-propyl]]-10*H*-phenothiazine dimaleate (1d). Perphenazine-d_6 dimaleate (1d) was prepared (63% yield) from 7b by the method described for 1c: m.p. and TLC as

for 1c; PMR(free base, $CDCl_3$): δ 1.72-2.00(m,2H,propyl central CH_2), 2.28-2.63(m,7H,CH_2-piperazine,piperazine CH_2 and O-H), 3.54(t,2H,CH_2-O,J=5Hz), 3.85(t,2H,CH_2-phenothiazine,J=6.5Hz), 6.56-7.19(m,7H,aromatic H); EIMS: 409/411($M^{+\cdot}$)(55/16), 378/380(19/6), 246/248(79/33), 233/235(100/31), 232/234 (62/43), 149(66), 120(40), 98(72).

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