Synthesis of Deuterium-Labeled Fluphenazine

H. UMESHA SHETTY, EDWARD M. HAWES ˣ, and KAMAL K. MIDHA

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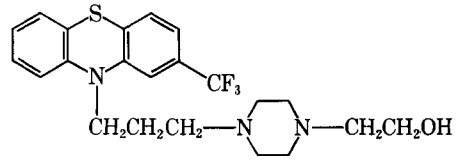
Abstract □ The propylpiperazine side chain of fluphenazine has been labeled with two, four, and six deuterium atoms by lithium aluminum deuteride reduction of the appropriate ester or imide. The γ-carbon of the propyl group was labeled with two deuterium atoms by reduction of 10- (2-methoxycarbonylethyl) -2-trifluoromethyl-10*H*-phenothiazine, while four deuterium atoms were incorporated into the piperazine ring by reduction of 10-[3-(3,5-dioxo-1-piperazinyl)propyl]-2-trifluoromethyl-10*H*-phenothiazine. The latter reduction gave the d_4-labeled *N*-deshydroxyethyl metabolite of fluphenazine.

Keyphrases □ Fluphenazine—synthesis of deuterium-labeled analogues, propylpiperazine side chain □ Synthesis—deuterium-labeled fluphenazine, propylpiperazine side chain

The quantitation of phenothiazine drugs in the plasma of patients under treatment is difficult due to low plasma concentrations, drug instability, and adsorptive losses. In the case of the piperazine-type phenothiazines, such as fluphenazine (I), the low doses used compound these



I

problems. In patients receiving normal therapeutic doses of the fatty acid ester depot formulations (fluphenazine decanoate or enanthate) intramuscularly, the plasma steady-state levels have been found to be in the low nanogram/milliliter range (1, 2) by radioimmunoassay (RIA). However, such biological methods of analysis have doubtful specificity and need to be certified by sensitive chemical methods. Thus, to verify the RIA method developed in these laboratories (3), which is capable of quantitating 0.25 ng of fluphenazine/mL of plasma using 200-μL plasma aliquots, we wanted to develop a GC–MS procedure. Such methods potentially have sensitivity comparable to RIA and, in general, can be performed using small plasma samples.

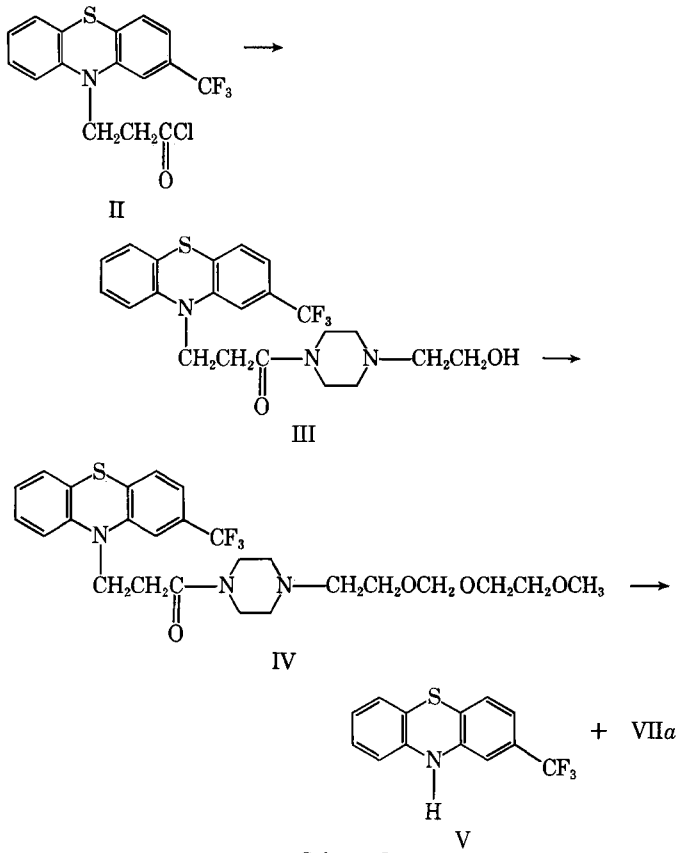
A stable isotope analogue of fluphenazine was needed as a reliable internal standard to obtain the required sensitivity of the GC–MS spectrometric procedure. Also, further stable isotopes of fluphenazine were required for administration to animals or humans by one or two routes so as to allow reliable pharmacokinetics, including absolute and relative bioavailability data, to be obtained, with the analysis of plasma concentrations by GC–MS using a selected ion monitoring technique. This would enable the definitive pharmacokinetics of fluphenazine to be determined using fewer administrations and far fewer individuals than would otherwise be possible.

This paper describes the synthesis of fluphenazine with two, four, and six deuterium atoms in the propylpiperazine side chain. This labeling site was chosen since it is generally not metabolically lost and allows variation in the number of deuterium atoms added.

RESULTS AND DISCUSSION

The syntheses of the piperazine-type phenothiazines, prochlorperazine (4) and trifluoperazine (5), labeled in the propylpiperazine side chain with two, four, and six deuterium atoms have been previously reported from these laboratories. Two deuterium atoms were incorporated in the propyl chain by reduction of a carbonyl group α to the piperazine ring. In a similar fashion we initially attempted to synthesize fluphenazine-d_2 by lithium aluminum deuteride reduction of the side-chain amide (III), obtained from the previously reported 2-trifluoromethyl-10*H*-phenothiazine-10-propionyl chloride (II) (5). Since only starting material was isolated from this reaction, and as lithium aluminum hydride is known to react with alcohol groups, it was decided to protect the alcohol group with 2-methoxyethoxymethyl (MEM) chloride. However, the protected alcohol (IV) on lithium aluminum hydride reduction gave none of the desired material, but instead 2-trifluoromethyl-10*H*-phenothiazine (V) and 10-(3-hydroxypropyl)-2-trifluoromethyl-10*H*-phenothiazine (VII*a*) (Scheme I). Similar reverse Michael reactions have been observed on attempted lithium aluminum hydride reduction of substituents in the N-10 side chain of phenothiazines: 2-chloro-10(2-cyanoethyl)-10*H*-phenothiazine yielded 2-chlorophenothiazine (6), while trace amounts of V and VII*a* were also obtained in the reduction of the intermediate 10-[3-(4-methyl-1-piperazinyl)-3-oxopropyl]-2-trifluoromethyl-10*H*-phenothiazine used in the synthesis of trifluoperazine-d_2[1].

The synthesis of fluphenazine-d_2 was successfully carried out as outlined in Scheme II (VI→VII*b*→VIII*b*→I*a*). The key reduction step used to incorporate deuterium, involving the conversion of 10-(2-methoxy-



Scheme I

[1] H. U. Shetty, E. M. Hawes, and K. K. Midha, unpublished observations, subsequent to the publication of Ref. 5.

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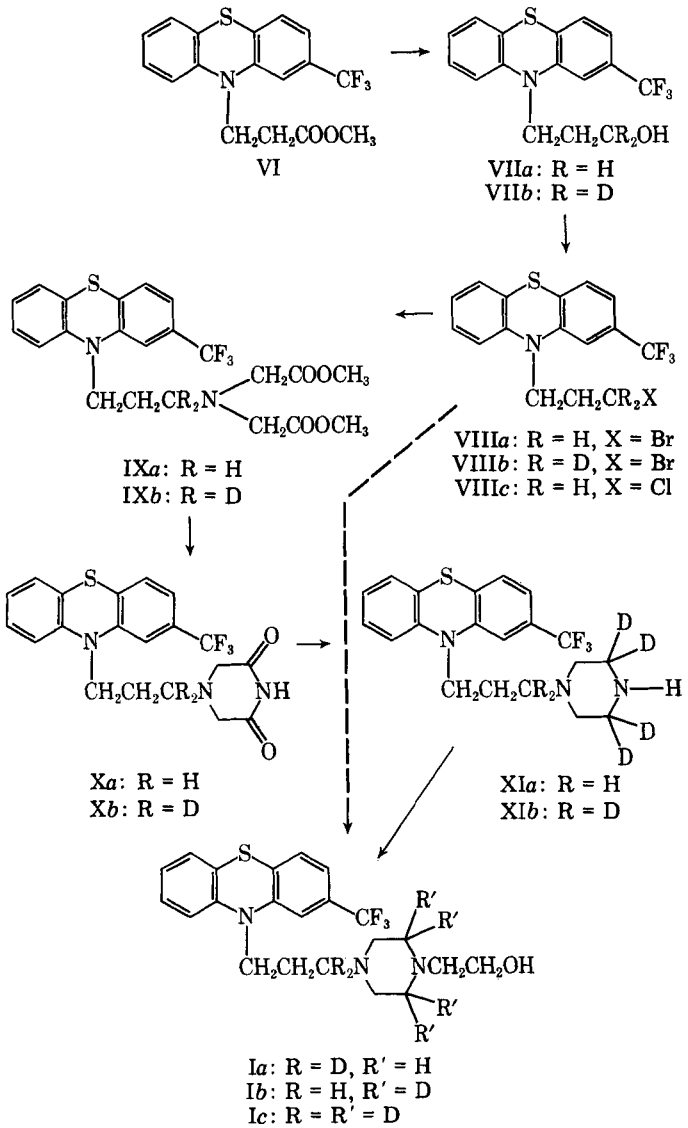
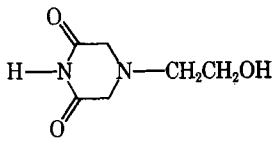


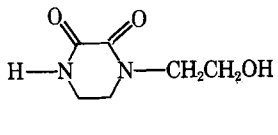
Scheme II—Synthesis of fluphenazine-d_2, -d_4, *and* -d_6.

carbonylethyl)-2-trifluoromethyl-10*H*-phenothiazine (VI) (7) to 2-trifluoromethyl-10*H*-phenothiazine-10-propanol (VII*a*) with lithium aluminum hydride has not been previously reported, although another route to this alcohol product is referred to in the patent literature (8). The final two steps, subsequent to the incorporation of deuterium, proceeded smoothly with the involvement of the newly reported bromopropyl compound (VIII*a*), synthesized by bromination of the alcohol with triphenylphosphine and *N*-bromosuccinimide (9), rather than the chloropropyl analogue (VIII*c*) invariably used in phenothiazine syntheses of this type.

For the previously reported syntheses of the d_4-labeled methylpiperazine-type phenothiazines, prochlorperazine (4) and trifluoperazine (5), the key intermediate involved was 1-methyl[3,3,5,5-$^2H_4$]piperazine, synthesized by lithium aluminum deuteride reduction of 1-methyl-3,5-piperazinedione. To synthesize labeled 2-hydroxyethylpiperazine-substituted phenothiazines in a similar fashion, suitable previously reported diketopiperazines appeared to be 1-(2-hydroxyethyl)-3,5-piperazinedione (XII) (10) and 1-(2-hydroxyethyl)-2,3-piperazinedione (XIII) (11). The former was obtained as a crude oil, which failed to distill under high vacuum, despite the report to the contrary (10); all subsequent attempts at purification failed to yield a sample of XII in a state suitable



XII



XIII

for the eventual synthesis of deuterium-labeled material for use as an internal standard and/or human administration. The 2,3-dione (XIII) was obtained in a pure form, but subsequent lithium aluminum hydride reduction gave none of the desired 1-(2-hydroxyethyl)piperazine even though none of the starting material (XIII) was recovered on GC of the reaction residue. This is hardly surprising in view of the report that under similar reaction conditions, the parent compound (piperazine-2,3-dione) was reduced quantitatively with ring opening to 1,2-diaminoethane (12).

The route utilized to synthesize fluphenazine-d_4 (Scheme II: VIII*c*→IX*a*→X*a*→XI*a*→I*b*) involves a novel route to piperazine-type phenothiazines. The piperazine ring was built stepwise onto the propyl side chain by amination of 10-(3-chloropropyl)-2-trifluoromethyl-10*H*-phenothiazine (VIII*c*) (13) with methyl iminodiacetate, followed by alkaline hydrolysis and subsequent urea fusion. The imide (X*a*) so formed was subsequently reduced with lithium aluminum deuteride to afford the labeled *N*-desalkyl metabolite of fluphenazine and trifluoperazine (XI*a*). Finally, alkylation gave greater yields with 2-bromoethanol than using ethylene oxide as reagent, to afford the desired fluphenazine-d_4 (I*b*). For each of the six steps involved in this synthesis, including the initial alkylation of 2-trifluoromethylphenothiazine with 1-bromo-3-chloropropane, yields were at least 70%. The synthesis of fluphenazine-d_6 was carried out in a similar fashion (VIII*b*→IX*b*→X*b*→XI*b*→I*c*) starting with the 10-(3-bromopropyl)-2-trifluoromethyl-10*H*-phenothiazine-d_2 (VIII*b*) discussed above.

The isotopic purity of the labeled purified products was determined by electron-impact mass spectrometry. The ratio for the molecular ions $^2H_0/^2H_n$ was determined to be 8.11, 3.49, and 0.01%, for the di-(n = 2) (I*a*), tetra-(n = 4) (I*b*), and hexa-(n = 6) (I*c*) deuterated fluphenazine, respectively. This purity of fluphenazine-d_6 is sufficient for its use as a reliable internal standard in GC–MS analyses and pharmacokinetic studies. However, in the case of fluphenazine-d_2 and -d_4 appropriate contribution from isotopes will be required, which can be easily carried out by the use of computerized data systems. These studies will be reported elsewhere.

EXPERIMENTAL[2]

10- [3-(4-Hydroxyethyl-1-piperazinyl)-3-oxopropyl] -2-trifluoromethyl-10*H*-phenothiazine (III)—To a solution of 2-hydroxyethylpiperazine (0.325 g, 2.5 mmol) in 10 mL of dry acetone, cooled to −50°C in a dry-ice bath, was added dropwise over 30 min a solution of 2-trifluoromethyl-10*H*-phenothiazine-10-propionyl chloride (II) (5) (0.715 g, 2.0 mmol) in 10 mL of dry acetone. The reaction mixture was stirred for 1 h, during which time the mixture was allowed to attain room temperature. The residue left after evaporation of the solvent was dissolved in methanol (10 mL), triturated with 1 M NaOH (10 mL), and the resulting suspension was heated on a water bath. The methanol was evaporated off and the resultant mixture was extracted with chloroform (3 × 20 mL). The chloroform extracts were combined, dried over magnesium sulfate, and evaporated under reduced pressure to afford a pale yellow liquid, which solidified on standing. Recrystallization from benzene–hexane resulted in 0.76 g (84%) of fine white needles, mp 111–112°C; ^{1}H-NMR ($CDCl_3$): δ 2.02–2.88 (m, 10, piperazine methylene and CH_2-piperazine), 3.00–3.85 (m, 5, CH_2CO and CH_2OH), 4.22 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.6–7.4 ppm (m, 7, aromatic); MS: m/z 451 ($M^{+\cdot}$, 100%), 420(48), 320(24), 280(52), 266(30), 248(20), and 127(10).

Anal.—Calc. for $C_{22}H_{24}F_3N_3O_2S$: C, 58.52; H, 5.36; N, 9.31. Found: C, 58.75; H, 5.31; N, 9.27.

10-[3-(4-Methoxyethoxymethoxyethyl-1-piperazinyl)-3-oxopropyl]-2-trifluoromethyl-10*H*-phenothiazine (IV)—A mixture of III (0.451 g, 1 mmol), β-methoxyethoxymethyl chloride (0.249 g, 2 mmol), and triethylamine (0.202 g, 2 mmol) in dry acetonitrile (5 mL) was heated at reflux for 12 h. The solvent was removed, and the residue was partitioned between ether and water. The ether layer was washed with saturated brine solution and dried over anhydrous magnesium sulfate. Re-

[2] Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. All TLC were performed using Eastman Chromatogram Sheets, type 13254 (silica gel with fluorescent indicator); spots were observed under shortwave UV light. NMR spectra were determined on a Varian T-60 instrument with tetramethylsilane as internal reference. Low-resolution electron-impact mass spectra were routinely recorded on a VG Micromass MM16F instrument at 70 eV equipped with a VG 2025 data system. Microanalyses for samples dried over phosphorus pentoxide at 60°C under reduced pressure were performed by Mr. R. E. Teed, Department of Chemistry and Chemical Engineering, University of Saskatchewan. Lithium aluminum deuteride (>99% deuterium) was obtained from Merck Sharp and Dohme, Dorval, Quebec, and all other chemicals from Aldrich Chemical Co., Montreal, Quebec.

moval of the ether afforded an oil, which was passed through an alumina column (ether). Evaporation of the ether gave 0.51 g (95%) of the desired product as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 2.22–3.00 (m, 10, piperazine methylene and CH_2-piperazine), 3.20–3.87 (m, 13, CH_2CO and CH_2O-$CH_2OCH_2CH_2OCH_3$), 4.31 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.7–7.4 ppm (m, 7, aromatic); MS: m/z 539 ($M^{+\cdot}$, 66%), 464(12), 420(100), 407(15), 320(37), 280(62), 266(38), 246(28), 127(35), and 99(24).

Anal.—Calc. for $C_{26}H_{32}F_3N_3O_4S$: C, 57.86; H, 5.97; N, 7.78. Found: C, 57.57; H, 5.97; N, 7.66.

Reduction of IV with Lithium Aluminum Hydride—To a suspension of lithium aluminum hydride (0.019 g, 0.5 mmol) in dry tetrahydrofuran (2 mL) was added dropwise a solution of IV (0.270 g, 0.5 mmol) in dry tetrahydrofuran (2 mL). After heating at reflux for 3 h with stirring, moist ether (10 mL) and water (0.5 mL) were successively added dropwise with stirring to the cooled reaction mixture. The precipitated inorganic material was filtered off, washed with ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the ether afforded a residue which on TLC (benzene–ethyl acetate 9:1) showed two spots corresponding to authentic samples of 2-trifluoromethyl-10*H*-phenothiazine (V) (R_f 0.81) and 10-(3-hydroxypropyl)-2-trifluoromethyl-10*H*-phenothiazine (VII*a*) (R_f 0.46). These authentic samples (V and VII*a*) gave identical GC retention times and electron-impact MS as the only two significant peaks resulting from GC–MS of the crude reaction mixture.

10-(3-Hydroxypropyl)-2-trifluoromethyl-10*H*-phenothiazine (VII*a*)—A solution of 1.765 g (5 mmol) of 10-(2-methoxycarbonylethyl)-2-trifluoromethyl-10*H*-phenothiazine (VI), bp 162–164°C/0.04 mm Hg [lit. (7) bp 172–175°C/55 μ] prepared as previously reported (7), in 10 mL of dry ether was added dropwise over 30 min to a magnetically stirred suspension under dry nitrogen of lithium aluminum hydride (0.190 g, 5 mmol) in 10 mL of dry ether at 0°C. After stirring for an additional hour at room temperature, the reaction mixture was heated at reflux for 30 min. Moist ether (10 mL) and 10% HCl (10 mL) were then successively added dropwise with stirring to the reaction mixture maintained at 0°C. The ether layer was separated, and the aqueous layer was washed with 10 mL of ether. The combined ether layers were dried (magnesium sulfate), evaporated, and the oily residue was passed through a neutral alumina column (ether). Evaporation of the solvent gave 1.531 g (94%) of a pale yellow oil which solidified on standing. An analytical sample was obtained by recrystallization from benzene–hexane, as pale yellow scales, mp 61–62°C; ^{1}H-NMR ($CDCl_3$): δ 1.62–2.30 (m, 3, propyl central methylene and OH), 3.76 (t, 2, J = 6 Hz, CH_2O), 4.06 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.78–7.48 ppm (m, 7, aromatic); MS: m/z 325 ($M^{+\cdot}$, 82%), 280(61), 266(100), and 248(24).

Anal.—Calc. for $C_{16}H_{14}F_3NOS$: C, 59.06; H, 4.34; N, 4.31. Found: C, 58.88; H, 4.34; N, 4.32.

10-(3-Hydroxy[3,3-$^2H_2$]propyl)-2-trifluoromethyl-10*H*-phenothiazine (VII*b*)—This compound was prepared (95% yield) by the lithium aluminum deuteride reduction of VI using the method described for VII*a*, mp 60–61°C and not depressed when mixed with VII*a*; ^{1}H-NMR ($CDCl_3$): δ 1.72 (s, 1, OH), 2.02 (t, 2, J = 7 Hz, CH_2CD_2), 4.04 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.65–7.42 ppm (m, 7, aromatic); MS: m/z 327 ($M^{+\cdot}$, 85%), 280(68), 266(100), and 248(25).

10-(3-Bromopropyl)-2-trifluoromethyl-10*H*-phenothiazine (VIII*a*)—To a stirred solution of 0.651 g (2 mmol) of VII*a* and 0.787 g (3 mmol) of triphenylphosphine in 5 mL of dry acetonitrile was added dropwise over 15 min a solution of 0.534 g (3 mmol) of *N*-bromosuccinimide in 5 mL of dry acetonitrile. The mixture was then stirred at room temperature for 1 h, the solvent was removed under reduced pressure, and the residue was partitioned between benzene and water. The organic phase was washed several times with water and dried over anhydrous magnesium sulfate. The residue left after removal of the solvent was digested with hexane (20 mL), cooled, and the precipitated triphenylphosphine oxide was removed by filtration and washed with *n*-hexane. The filtrate was passed through an alumina column, and on removal of solvent, the product was obtained as a white amorphous solid. Recrystallization from methanol afforded 0.670 g (86%) of white needles, mp 70–71°C; ^{1}H-NMR ($CDCl_3$): δ 2.32 (q, 2, J = 6 Hz, propyl central methylene), 3.56 (t, 2, J = 6 Hz, CH_2Br), 4.17 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.78–7.47 ppm (m, 7, aromatic); MS: m/z 389 ($M^{+\cdot}$, 38%), 387(38), 280(83), 266(100), and 248(45).

Anal.—Calc. for $C_{16}H_{13}BrF_3N_3S$: C, 49.49; H, 3.37; N, 3.61. Found: C, 49.72; H, 3.34; N, 3.61.

10-(3-Bromo[3,3-$^2H_2$]propyl)-2-trifluoromethyl-10*H*-phenothiazine (VIII*b*)—This compound was prepared (90% yield) from VII*b* by the method described for VIII*a*, mp as for VIII*a*; ^{1}H-NMR ($CDCl_3$): δ 2.27 (t, 2, J = 7 Hz, CH_2CD_2), 4.10 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.70–7.38 ppm (m, 7, aromatic); MS: m/z 391 ($M^{+\cdot}$, 73%), 389(73), 280(94), 266(100), and 248(32).

10-[[3-[4-(2-Hydroxyethyl)-1-piperazinyl]-[3,3-$^2H_2$]propyl]]-2-trifluoromethyl-10*H*-phenothiazine Dihydrochloride (I*a*)—A mixture of VIII*b* (0.781 g, 2 mmol) and 2-hydroxyethylpiperazine (0.521 g, 4 mmol) in methyl ethyl ketone was heated at reflux for 4 h. The solvent was removed under reduced pressure, and the residue was stirred with 10% HCl (20 mL). The acidic solution was washed with ether (3 × 10 mL), and the combined ether wash was extracted with 10% HCl (5 mL). The combined acid fractions were basified with sodium carbonate and extracted with ether (4 × 10 mL). The ether extracts were combined, washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The resulting pale yellow oil was dissolved in dry ether (10 mL), treated with ethereal HCl, and the solid which separated was recrystallized from absolute ethanol to afford 0.975 g (95%) of fluphenazine-d_2 dihydrochloride (I*a*), mp 235–237°C [lit. (8) unlabeled mp 235–237°C]. Mixed melting points with authentic nondeuterated samples (I), obtained commercially[3] or synthetically by amination of VIII*a*, were not depressed; TLC: R_f (acetone–ammonia, 100:1) 0.63; ^{1}H-NMR (free base, $CDCl_3$): δ 1.91 (t, 2, J = 7 Hz, CH_2CD_2), 2.28–2.87 (m, 10, piperazine methylene and CH_2-piperazine), 3.36 (s, 1, OH), 3.60 (t, 2, J = 5 Hz, CH_2O), 3.95 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.69–7.46 ppm (m, 7, aromatic); MS: m/z 439 ($M^{+\cdot}$, 24%), 408(27), 280(100), 266(21), 248(20), 173(10), 145(39), 115(28), 100(21), 98(14), and 72(34).

10-[3-(*N*,*N*-Dimethoxycarbonylmethyl)aminopropyl]-2-trifluoromethyl-10*H*-phenothiazine (IX*a*)—A mixture of 6.87 g (20 mmol) of 10-(3-chloropropyl)-2-trifluoromethyl-10*H*-phenothiazine (VIII*c*), mp 69–70°C [lit. (14) mp 70–71°C] prepared in 70% yield by adaptation of the procedure used for the 2-chlorophenothiazine analogue (13), 8.058 g (50 mmol) of iminodiacetic acid dimethyl ester (15), and 3.0 g (20 mmol) of sodium iodide was heated at reflux in 50 mL of methyl ethyl ketone for 24 h. The solvent was evaporated to leave an oily residue, which was dissolved in 15% HCl. The acid was washed with ether (2 × 20 mL) and then neutralized with sodium carbonate. The oil that separated was extracted into ether (3 × 30 mL), and the combined ether extracts were washed with water (2 × 10 mL), dried over anhydrous magnesium sulfate, and evaporated to leave an oily residue. Vacuum distillation gave 6.8 g (73%) of the desired product as a viscous yellow oil, bp 208–210°/0.5 mmHg; ^{1}H-NMR ($CDCl_3$): δ 1.88 (q, 2, J = 6 Hz, propyl central methylene), 2.82 (t, 2, J = 6 Hz, CH_2-side chain N), 3.45 (s, 4, CH_2CO), 3.6 (s, 6, OCH_3), 3.99 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.6–7.38 ppm (m, 7, aromatic); MS: m/z 468 ($M^{+\cdot}$, 12%), 307(13), 266(18), 248(23), 174(30), and 116(100).

Anal.—Calc. for $C_{22}H_{23}F_3N_2O_4S$: C, 56.39; H, 4.94; N, 5.98. Found: C, 56.29; H, 5.06; N, 5.98.

10-[3-(*N*,*N*-Dimethoxycarbonylmethyl)amino[3,3-$^2H_2$]propyl]-2-trifluoromethyl-10*H*-phenothiazine (IX*b*)—This was prepared (93% yield) from VIII*b* by the method decribed for IX*a*. The product was purified by silica gel chromatography (ether); ^{1}H-NMR ($CDCl_3$): δ 1.84 (t, 2, J = 7 Hz, CH_2CD_2), 3.46 (s, 4, CH_2CO), 3.61 (s, 6, OCH_3), 4.0 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.61–7.34 ppm (m, 7, aromatic); MS: m/z 470 ($M^{+\cdot}$, 20%), 307(13), 266(18), 248(14), 176(14), and 118(100).

10-[3-(3,5-Dioxo-1-piperazinyl)propyl]-2-trifluoromethyl-10*H*-phenothiazine (X*a*)—Ester IX*a* (4.685 g, 10 mmol) was hydrolyzed by treatment with aqueous methanol (50 mL of methanol and 50 mL of water) containing sodium hydroxide (1.60 g, 40 mmol), heated under reflux on a steam bath for 1 h. The cooled solution was diluted with water (50 mL), and the pH was adjusted to 3.0. The precipitated product was filtered, washed with water, and dried to afford 4.14 g (94%) of the acid intermediate, mp 128–129°C. The finely powdered acid (4.4 g, 10 mmol) and urea (0.66 g, 11 mmol) were mixed, heated to 175°C on an oil bath, and held at this temperature for 2 h with stirring. The mixture was cooled, and the solidified product was dissolved in boiling ethanol, treated with activated charcoal, and filtered. On cooling 3.0 g (71%) of the desired product (X*a*) crystallized as pale yellow needles, mp 151–152°C; ^{1}H-NMR (DMSO-d_6): δ 1.84 (q, 2, J = 7 Hz, propyl central methylene), 3.28 (s, 6, piperazinedione methylene and CH_2-piperazinedione), 3.98 (t, 2, J = 7 Hz, CH_2-phenothiazine), 6.65–7.40 (m, 7, aromatic), and 10.9 ppm (s, 1, NH); MS: m/z 421 ($M^{+\cdot}$, 100%), 306(23), 280(39), 266(78), 248(42), 155(46), 127(63), 99(18), 83(25), and 71(42).

Anal.—Calc. for $C_{20}H_{18}F_3N_3O_2S$: C, 57.00; H, 4.30; N, 9.97. Found: C, 57.16; H, 4.37; N. 9.88.

10-[3-(3,5-Dioxo-1-piperazinyl)[3,3-$^2H_2$]propyl]-2-trifluoromethyl-10*H*-phenothiazine (X*b*)—This was prepared (68% yield) from

[3] A gift from Squibb Canada Inc., Montreal, Quebec.

ester IX*b* by the method described for X*a*, mp as for X*a*; ^{1}H-NMR (DMSO-d_6): δ 1.80 (t, 2, J = 7 Hz, CH_2CD_2), 3.24 (s, 4, piperazinedione methylene), 3.98 (t, 2, J = 7 Hz, CH_2-phenothiazine), 6.78–7.48 (m, 7, aromatic), and 10.9 ppm (s, 1, NH); MS: *m/z* 423 ($M^{+\cdot}$, 100%), 308(24), 280(46), 266(82), 248(46), 157(80), 129(69), 101(22), 85(25), and 73(26).

10-[[3-(1-[3,3,5,5-$^2H_4$]Piperazinyl)propyl]]-2-trifluoromethyl-10*H*-phenothiazine Dimaleate (XI*a*)—A solution of 1.264 g (3 mmol) of X*a* in 10 mL of dry tetrahydrofuran was added dropwise over 30 min to a stirred suspension of 0.504 g (12 mmol) of lithium aluminum deuteride in 10 mL of dry tetrahydrofuran at 0°C under nitrogen. After 2 h under reflux, 10 mL of moist ether and 2 mL of water 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 over anhydrous sodium sulfate, filtered, and evaporated to dryness. The yellow oily residue was dissolved in acetone (10 mL) and treated with maleic acid (0.812 g, 7 mmol) in acetone (5 mL). The dimaleate salt was filtered and recrystallized from ethanol to afford 1.4 g (74%) of XI*a*, mp 152–154°C. Mixed melting points with the authentic nondeuterated samples, obtained by the same route with lithium aluminum hydride or from a commercial source[4], were not depressed; TLC: R_f (benzene–methanol, 8:2) 0.5; ^{1}H-NMR (free base, $CDCl_3$): δ 1.40 (s, 1, NH), 1.91 (q, 2, J = 7 Hz, propyl central methylene), 2.35 (m, 6, CH_2-piperazine and piperazine-2,6-methylene), 3.95 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.62–7.4 ppm (m, 7, aromatic); MS: *m/z* 397 ($M^{+\cdot}$, 25%), 266(10), 248(10), 131(22), 103(84), 72(14), and 58(100).

10-[[3-(1-[3,3,5,5-$^2H_4$]Piperazinyl)[3,3-$^2H_2$]propyl]]-2-trifluoromethyl-10*H*-phenothiazine Dimaleate (XI*b*)—*N*-Deshydroxyethylfluphenazine-d_6 (XI*b*) was prepared (73% yield) by the lithium aluminum deuteride reduction of X*b* using the method described above for XI*a*, mp and TLC as for XI*a*; ^{1}H-NMR (free base, $CDCl_3$): δ 1.48 (s, 1, NH), 1.92 (t, 2, J = 7 Hz, propyl CH_2CD_2), 2.35 (s, 4, piperazine-2,6-methylene), 3.95 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.67–7.34 ppm (m, 7, aromatic); MS: *m/z* 399 ($M^{+\cdot}$, 23%), 266(10), 248(11), 133(25), 105(75), 74(16), and 60(100).

10-[[3-[4-(2-Hydroxyethyl)-1-[3,3,5,5-$^2H_4$]piperazinyl]propyl]]-2-trifluoromethyl-10*H*-phenothiazine Dihydrochloride (I*b*)—A mixture of XI*a* (0.397 g of free base, 1 mmol), 2-bromoethanol (0.125 g, 1 mmol) and potassium carbonate (0.138 g, 1 mmol) in dry methyl ethyl ketone (10 mL) was refluxed under dry nitrogen for 10 h. The solvent was removed under reduced pressure, and the residue was stirred with ether (10 mL). The ether layer was washed with water (2 × 5 mL) and dried over anhydrous sodium sulfate. The dried extract was then added to a short column of alumina, which was eluted with ether. The oily residue left after removal of the ether was dissolved in 2 mL of dry ether and treated with ethereal HCl. The precipitated dihydrochloride salt was recrystallized from absolute ethanol–ether to afford 0.365 g (71%) of fluphenazine-d_4 dihydrochloride (I*b*) as fine white needles, mp 232–234°C. A mixed melting point with an authentic[3] nondeuterated sample was not depressed; TLC: as for I*a*; ^{1}H-NMR (free base, $CDCl_3$): δ 1.88 (q, 2, J = 7 Hz, propyl central methylene), 2.20–2.83 (m, 9, propyl CH_2-piperazine, piperazine-2,6-methylene, ethyl CH_2-piperazine, and OH), 3.53 (t, 2, J = 5 Hz, CH_2O), 3.90 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.68–7.35 ppm (m, 7, aromatic); MS: *m/z* 441 ($M^{+\cdot}$, 17%), 410(18), 280(100), 266(14), 248(18), 161(13), 147(31), 117(22), 103(11), 102(10), and 72(25).

10-[[3-[4-(2-Hydroxyethyl)-1-[3,3,5,5-$^2H_4$]piperazinyl]-[3,3-$^2H_2$]propyl]]-2-trifluoromethyl-10*H*-phenothiazine Dihydrochloride (I*c*)—Fluphenazine-d_6 (I*c*) was prepared (74% yield) from XI*b* by the method described above for I*b*; mp and TLC as for I*b*; ^{1}H-NMR (free base, $CDCl_3$): δ 1.86 (t, 2, J = 7 Hz, propyl CH_2CD_2), 2.11–2.70 (m 6, piperazine-2,6-methylene and CH_2-piperazine), 3.53 (t, 2, J = 5 Hz, CH_2O), 3.90 (t, 2, J = 7 Hz, CH_2-phenothiazine), and 6.64–7.28 ppm (m, 7, aromatic); MS: *m/z* 443 ($M^{+\cdot}$, 27%), 412(28), 280(100), 266(25), 248(21), 163(16), 149(43), 119(30), 104(13), 103(13), 102(17), and 74(37).

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