SYNTHESIS OF DEUTERIUM LABELLED FLUPHENAZINE UTILISING BORANE REDUCTION

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SUMMARY

Two new procedures are described for the preparation of di- and tetra-deuterated 10-[[3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl]]-2-trifluoromethyl-10*H*-phenothiazine (fluphenazine). Deuterium was introduced in either the 1- or the 1- and 3-positions of the propyl side chain by reduction with deuterated borane in tetrahydrofuran of the appropriately substituted N-10 amide or amido ester. The isotopic purity of the synthesized deuterated products was greater than 99%.

Key Words: Antipsychotic, fluphenazine, deuterium labelling.

INTRODUCTION

The syntheses of piperazine-type phenothiazine antipsychotic agents, namely fluphenazine (1), perphenazine (2), prochlorperazine (3) and trifluoperazine (4), with two, four and six deuterium atoms in the propyl and/or piperazine groups of the N-10 side chain were previously reported. These labelled compounds have been utilised as true internal standards in GC-MS assays (5,6), as well as in metabolic (6,7) and pharmacokinetic (6,8) studies. For these ongoing studies deuterated analogs of piperazine-type phenothiazine antipsychotic agents with the label solely in the propyl chain were required. This site has been demonstrated to be less prone than the rest of the molecule to metabolic attack (9). It is known that protons are readily lost from the 2-position of the propyl chain in organic synthetic procedures involving acidic or basic treatments and in the electron impact mass spectral fragmentations of the products. Therefore, it seemed preferable to explore further synthetic methods to deuterated piperazine-type phenothiazine antipsychotic agents with the label

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restricted to the 1- and 3-positions of the propyl chain. In the previous reports (1-4) two deuterium atoms were incorporated in the 3-position of this propyl chain. This paper describes the synthesis of fluphenazine (Figure I, 6a) specifically labelled with two or four deuterium atoms in the 1- or 1- and 3-positions of the propyl side chain, respectively. Deuterium labelled fluphenazine is required for ongoing collaborative studies involving this drug (10).

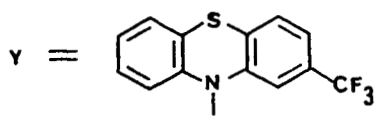
DISCUSSION

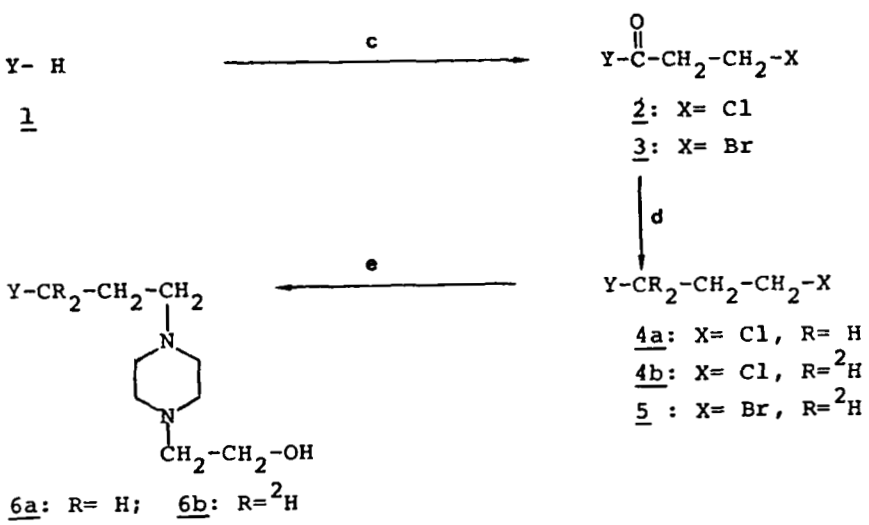
An important step in the synthetic routes reported here to the preparation of dideuterated and tetradeuterated fluphenazine involved deuterated borane reduction of the appropriate N-10 acylated phenothiazine derivative (Figures I,II). In the previous reports (1-4) to the synthesis of deuterated piperazine-type phenothiazine antipsychotic agents, deuterium was introduced by lithium aluminium deuteride reduction of the appropriate amide, ester or imide. However, as expected (11), this reagent results in various products, including retro-Michael products on attempted reduction of N-10 acylated phenothiazine derivatives.

The selective borane reduction of simple carboxylic acid amides to amines in the presence of less susceptible groups such as esters, bromides or chlorides, is well established (11). Also there is a report to the synthesis of deuterium labelled analogues of tricyclic antidepressant drugs where the label in the 1-position of the propyl side chain was introduced by reduction of the appropriate acylated iminodibenzyl compound with deuterated borane (12). However, we are unaware of previous applications of this reagent to the synthesis of deuterium labelled analogues of phenothiazine antipsychotic agents. It is an important attribute of the synthetic schemes reported here that relatively mild conditions are involved in the formation and borane reduction of the N-10 acylated phenothiazines, since the loss of the side chain is commonly encountered in reactions involving these compounds.

In the previous report to dideuterated fluphenazine the deuterium atoms were incorporated at the 3-position of the propyl chain by a five step synthetic

sequence (1). We now report by a three step sequence (Figure I) the synthesis of the analogue 6b with the two deuterium atoms incorporated at the 1-position of the propyl chain. This simple sequence, analogous to the previous report (12) to the synthesis of the dideuterated analogues of the tricyclic antidepressant drugs, desipramine and imipramine, involved an initial acylation of 2-trifluoromethyl-10*H*-phenothiazine with either 3-chloropropionyl chloride or 3-bromopropionyl chloride (1→2,3). The *N*-10 acylated compounds, 2 and 3, were treated with deuterated borane in tetrahydrofuran and the resultant reduced products, 4b and 5, then treated with 2-hydroxyethylpiperazine to obtain flu-





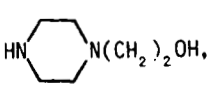
c: $ClCCH_2CH_2Cl$ or $ClCOCH_2CH_2Br, C_6H_6$; **d**: BH_3 or B^2H_3, THF; **e**:  , only with 4 KI, $CH_3COC_2H_5$.

Figure I. Synthesis of [$^2H_2$]fluphenazine.

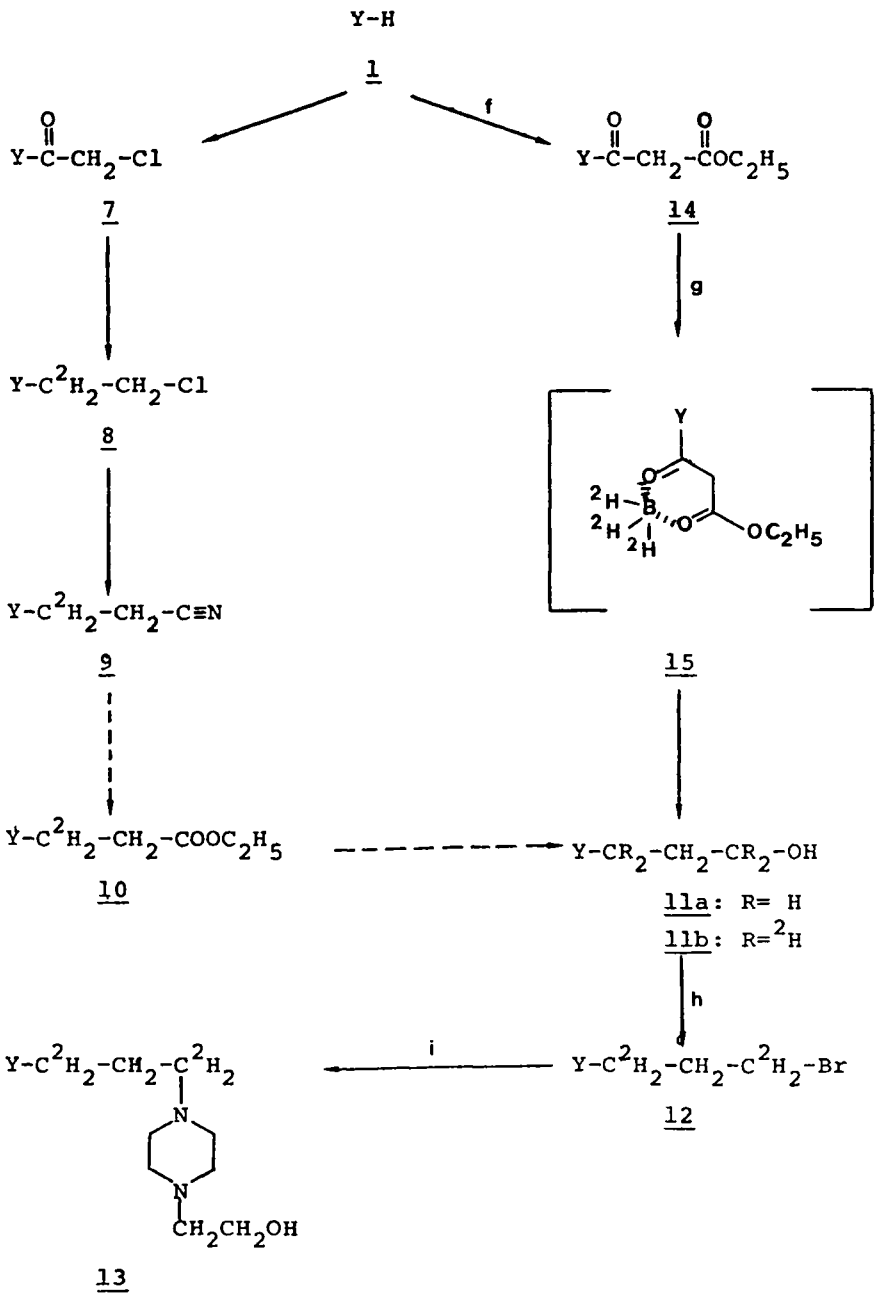
phenazine-1^1-$^2H_2$ (6b). The desired deuterated product was obtained in 44% overall yield for the three step synthetic sequence involving the chloroalkyl

intermediates.

We initially attempted to synthesise tetradeuterated fluphenazine by a multistep sequence (Figure II, 1→ 7→ 8→ 9→ 10→ 11b→ 12→ 13). This sequence firstly involved the acylation of 2-trifluoromethyl-10*H*-phenothiazine (1) with chloroacetyl chloride, followed by reduction of the acylated product 7 with deuterated borane to obtain the 2-chloroethyl compound 8 in good yield. However, the attempted conversion of this latter compound to the cyanide 9 under several conditions resulted in only low yields of the desired compound, the retro-Michael product 1 being the major product. Therefore, this multistep synthetic sequence was not investigated any further.

A novel synthetic scheme was developed for the synthesis of tetradeuterated fluphenazine (Figure II, 1→ 14→ 11b→ 12→ 13). Thus, the amido ester 14, obtained by *N*-10 acylation of 2-trifluoromethyl-10*H*-phenothiazine (1) with ethylmalonyl chloride, was reduced with deuterated borane to obtain the desired tetradeuterated alcohol 11b in 99.83% isotopic purity. Therefore, not only the amide functional group, but also the ester function was reduced in one step. It is hypothesised that this rare reduction by borane of an ester group resulted since six-membered ring intermediates, such as 15, increased the electrophilic nature of the carbonyl carbon atom. That reduction of both amide and ester functional groups had occurred was verified by examination of the EIMS and ^{1}HNMR spectra of the products resulting from the reduction of 14 with borane and deuterated borane. Also the anticipated shift of four mass units in the base peak (molecular ion) was seen on comparison of the EIMS of the non-deuterated alcohol 11a and the deuterated alcohol 11b. The deuterated alcohol 11b was subsequently brominated with triphenylphosphine and N-bromosuccinimide, while displacement of the bromine atom of the resultant product 12 by 2-hydroxyethylpiperazine resulted in the required fluphenazine-1^{1},3^{1}-^{2}H$_{4}$ (13). The overall yield of the four step synthetic sequence was 37%.

The isotopic purity of the labelled purified products was determined by GC-MS of the TMS derivative of the compound, where a single ion formed from the loss of CH_2OTMS from the parent ion was monitored. The $^{2}H_0/^{2}H_n$ ratios of these



f: Cl-CCH$_2$COC$_2$H$_5$, C$_6$H$_6$; g: BH$_3$ or B^{2}H$_3$, THF; h: NBS, (C$_6$H$_5$)$_3$P, CH$_3$C≡N;
1: HN⟨⟩N-(CH$_2$)$_2$OH, CH$_3$COC$_2$H$_5$

Figure II. Approaches to the synthesis of [^{2}H$_4$]fluphenazine

ions were determined to be 0.38 and 0.19% for the fluphenazine-1^{1}-$^{2}H_2$ and fluphenazine-1^{1},3^{1}-$^{2}H_4$, respectively. This purity is sufficient for their use in metabolic and pharmacokinetic studies, as well as true internal standards in GC-MS assays. Finally, the methods reported here to the synthesis of di-and tetra-deuterated analogues of fluphenazine with the label in the propyl side chain can be readily adapted for the synthesis of similarly labelled analogues of other piperazine-type phenothiazine antipsychotic agents, such as perphenazine, prochlorperazine and trifluoperazine, and aliphatic-type phenothiazine antipsychotic agents, such as chlorpromazine and triflupromazine.

EXPERIMENTAL

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Reactions were monitored on pre-coated fluorescent thin layer chromatographic (TLC) sheets (Kieselgel 60 F_{254}, E. Merck) and spots were observed under shortwave UV light. Infrared spectra (IR) were recorded on a Beckman Acculab 4 spectrophotometer. The proton nuclear magnetic resonance (^{1}HNMR) spectra were measured with a Varian T-60 spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ units (parts per million, ppm) relative to TMS. Electron impact mass spectra (EIMS) were recorded on a VG Micromass 7070HE instrument at 70eV equipped with a VG 2035 data system; relative intensity is noted in parentheses after each major fragment. Interface of this system with a Hewlett Packard 5790 gas chromatograph gave the GC-MS system: the chromatographic column was a 30 m Durabond-5 capillary column (0.32 mm i.d., 0.25 µm film thickness) (J & W Scientific Inc; Rancho Cordova, CA) and the MS was at 180°C source temperature. Elemental analysis were performed by Guelph Chemical Laboratories Ltd; Guelph, Ontario. Deuterated borane in tetrahydrofuran (>97.5% deuterium) was obtained from Ventron Corporation, Danvers, MA, and Merck, Sharp and Dohme, Dorval, Quebec. All other chemicals were obtained from Aldrich Chemical Co., Milwaukee, WI.

10-(3-Chloropropionyl)-2-trifluoromethyl-10*H*-phenothiazine (2). To a solution of 2-trifluoromethyl-10*H*-phenothiazine (1) (25.0g, 93.5 mmol) in dry benzene

(125 mL), cooled to 0-5°C, was added 3-chloropropionyl chloride (13.06g, 102.9 mmol) dropwise with stirring under a nitrogen atmosphere. The reaction mixture was refluxed for 24 h, allowed to attain room temperature and slowly added to ice water. The organic phase was separated, washed successively with 10% $NaHCO_3$ solution, water and saturated NaCl solution, and dried (Na_2SO_4). Removal of the solvent in vacuo gave 27.3g (82%) of a yellowish green solid, which recrystallised from benzene-hexane to afford 2, mp 78-79°C; IR(nujol):1670(C=O)cm^{-1}; ^{1}HNMR($CDCl_3$): δ2.70-3.20(m,2H,$C\underline{H}_2$-CO),3.82(t,2H,$C\underline{H}_2$-Cl),7.20-7.70(m,6H,aromatic H),7.93(broad s,1H,C_1-phenothiazine H); EIMS: m/z 359/357($M^{+\cdot}$,4/12),267(100), 266(51),93/91(3/7). Anal. Calcd. for $C_{16}H_{11}ClF_3NOS$:C,53.71;H,3.10; Cl,9.91; N,3.92. Found: C,54.10;H,3.22;Cl,10.23;N,3.97.

10-(3-Bromopropionyl)-2-trifluoromethyl-10*H*-phenothiazine (3). This was prepared from 1 and 3-bromopropionyl chloride by adaptation of the method described for 2. An oil was obtained, which recrystallised upon refrigeration to give 3, mp 80-81°C; ^{1}HNMR($CDCl_3$): δ2.86-3.23(m,2H,$C\underline{H}_2$-CO),3.75 (t,2H, $C\underline{H}_2$-Br),7.20-7.70(m,6H,aromatic H),7.83(broad s,1H,C_1-phenothiazine H);EIMS:m/z 403/401 ($M^{+\cdot}$,7/6),268(17),267(100),266(48). Anal. Calcd. for $C_{16}H_{11}BrF_3NOS$:C, 47.78; H,2.76;Br,19.86;N,3.48. Found: C,48.04;H,2.94;Br,19.58;N,3.49.

10-(3-Chloropropyl)-2-trifluoromethyl-10*H*-phenothiazine (4a). To an ice-cooled solution of borane in tetrahydrofuran (23.2 mL of 0.98M solution:22.7 mmol BH_3) was added the amide 2 (5g, 14.0 mmol) in portions with stirring under a nitrogen atmosphere. After completion of the addition the reaction mixture was allowed to attain room temperature and then refluxed for 2 h on an oil bath. Upon cooling to 0-5°C, excess borane and borane complexes were decomposed with the slow addition of 6N HCl (3.5 mL), and the solvent was removed in vacuo. The residue was basified (∿pH10) with 40% NaOH solution and extracted with ether. The organic phase was washed with water, followed by saturated NaCl solution, and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a solid, which was recrystallised from absolute ethanol to afford 4a (3.38 g, 70%), mp 70-71°C[lit.(13)mp 70-71°C]; ^{1}HNMR($CDCl_3$): δ1.93-2.43 (q,2H,J=6Hz, propyl central $C\underline{H}_2$),3.63(t,2H, J = 6Hz, CH_2-Cl),4.03(t,2H,J=6Hz, $C\underline{H}_2$-

phenothiazine), 6.76-7.96(m, 7H, aromatic H).

10-(3-Chloro[1,1-$^2H_2$]propyl)-2-trifluoromethyl-10*H*-phenothiazine (4b). This was prepared (60% yield) from 2 and deuterated borane in tetrahydrofuran by the method described for 4a, mp 73-75°C; ^{1}HNMR($CDCl_3$): δ 2.60 (t, 2H, J=6Hz, CH_2-CH_2-C^2H_2), 3.66(t, 2H, J=6Hz, CH_2-Cl), 6.80-7.40(m, 7H, aromatic H); EIMS:m/z 347/345($M^{+\cdot}$, 23/66), 266(100).

10-(3-Bromo[1,1-$^2H_2$]propyl)-2-trifluoromethyl-10*H*-phenothiazine (5). This was prepared (68% yield) from 3 and deuterated borane in tetrahydrofuran by the method described for 4a, mp 69-70°C [lit.(1)unlabelled mp 70-71°C]; ^{1}HNMR ($CDCl_3$): δ2.30(t, 2H, J=6Hz, CH_2-C^2H_2), 3.53(t, 2H, J=6Hz, CH_2-Br), 6.76-7.36(m, 7H, aromatic H); EIMS:m/z 391/389 ($M^{+\cdot}$, 70/67), 266(100).

10-[[3-[4-(2-Hydroxyethyl)-1-piperazinyl][1,1-$^2H_2$]propyl]]-2-trifluoromethyl-10*H*-phenothiazine (6b). A mixture of 4b (0.50 g, 1.45 mmol), 2-hydroxyethylpiperazine (0.471 g, 3.62 mmol) and a catalytic amount of KI was refluxed in ethyl methyl ketone (5 mL) for 24 h. The solvent was removed in vacuo, and the residue dissolved in 10% HCl (8 mL). The acidic solution was washed thoroughly with ether. The organic phase was separated and extracted with 10% HCl (2 x 10 mL). The combined acid fractions were basified with Na_2CO_3 and extracted with ether. The organic layer was washed with water, followed by saturated NaCl solution, and dried (Na_2SO_4). The solvent was removed in vacuo to afford a residual oil (0.61 g), which was dissolved in dry ether and treated with ethereal HCl. The resulting solid (0.62 g, 90%) was recrystallized from absolute ethanol to afford the dihydrochloride salt of 6b, mp 231-233°C [lit.(14) unlabelled mp 235-237°C]; ^{1}HNMR(free base, $CDCl_3$): δ1.83(t, 3H, J =6Hz, CH_2-C^2H_2), 2.10-2.70(m, 12H, piperazine CH_2 and CH_2-piperazine), 3.56(t and a broad s, 3H, J=6Hz, CH_2-OH), 6.67-7.20(m, 7H, aromatic H); EIMS:m/z 439($M^{+\cdot}$, 21), 407(12), 282(100), 266(11), 250(12), 173(10), 143 (39), 114(13), 100(17), 98(14). This compound 6b was also prepared (89% yield) from 5 and 2-hydroxyethylpiperazine using the procedure described for 13.

10-(2-Ethoxycarbonylacetyl)-2-trifluoromethyl-10*H*-phenothiazine (14). To a cooled (0-5°C) solution of 2-trifluoromethyl-10*H*-phenothiazine (1) (50.0 g,

187.1 mmol) in dry benzene (400 mL) was added ethyl malonyl chloride (15) (30.98 g, 205.8 mmol) dropwise with stirring under a nitrogen atmosphere. The reaction mixture was maintained at reflux for 17 h. The hot reaction mixture was carefully added to ice cold water with stirring. The organic phase was separated and successively washed with water and saturated NaCl solution and dried (Na_2SO_4). Removal of benzene in vacuo afforded a viscous oil (72.0 g), which was used in the subsequent step without further purification. A small amount was purified by column chromatography (silica column with chloroform as eluent); IR(neat):1740(ester C=O),1685(amide C=O)cm^{-1}; ^{1}HNMR($CDCl_3$): δ 1.25 (t,3H,J =7Hz,CH_3),3.56(s,2H,CH_2-CO),4.20(q,2H,J=7Hz, CH_2-O),7.20-7.70(m,6H, aromatic H),7.92 (broad s, 1H,C_1-phenothiazine H);EIMS:m/z 381($M^{+\cdot}$,3),267(29), 266(18),85(77),83(100),47(28).

10-(3-Hydroxypropyl)-2-trifluoromethyl-10*H*-phenothiazine (11a). To an ice-cooled solution of borane in tetrahydrofuran (17.6 mL of 0.98 M solution :17.2 mmol BH_3) was added dropwise a solution of the amido ester 14 (4.689 g, 12.3 mmol) in dry tetrahydrofuran (5 mL) with stirring under a nitrogen atmosphere. The reaction mixture was subsequently treated and worked up as for the preparation of 4a. However, in the work-up, removal of the ether in vacuo afforded an oil, which was passed through a silica column with chloroform as eluent. Evaporation of the appropriate fraction of eluate (TLC analysis) gave the previously reported (1) 11a, as a pale yellow oil (2.92 g, 73%); ^{1}HNMR($CDCl_3$): δ 1.99(m,2H,J = 6Hz,propyl central CH_2),2.43(s,1H,OH),3.68(t,2H,J=6Hz,CH_2-O), 3.98(t,2H,J=6Hz,CH_2-phenothiazine),6.73-7.47(m,7H,aromatic H).

10-(3-Hydroxy [1,1,3,3 -$^2H_4$]propyl)-2-trifluoromethyl-10*H*-phenothiazine (11b). This was prepared (46% yield) from 14 and deuterated borane in tetrahydrofuran (1.0 M solution) by the method described for 11a; ^{1}HNMR ($CDCl_3$): δ1.96(broad s,3H,CH_2 and OH),6.76-7.40(m,7H,aromatic H); EIMS:m/z 329 ($M^{+\cdot}$,100),282 (45),266(59),250(17).

10-(3-Bromo [1,1,3,3-$^2H_4$] propyl)-2-trifluoromethyl-10*H*-phenothiazine (12). This compound was prepared by an improved modification of the previously reported method for the synthesis of the non-deuterated compound (1). To a

stirred solution of the alcohol 11 (0.928 g, 2.8 mmol) and triphenylphosphine (1.108 g, 4.2 mmol) in acetonitrile (10 mL) (dried over molecular sieves) was added dropwise a solution of *N*-bromosuccinimide (0.752 g, 4.2 mmol) in dry acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 1 h. After removal of the solvent in vacuo, the residue was passed through a silica column with chloroform as eluent. Evaporation of the appropriate fraction of the eluate (TLC analysis) gave 1.01 g (90%) of 12, mp 70-71°C [lit. (1) unlabelled mp 70-71°C]; ^{1}HNMR($CDCl_3$): δ2.20(broad s,2H,$C\underline{H}_2$),6.70-7.30 (m,7H,aromatic H); EIMS: m/z 393/391($M^{+\cdot}$,72/73),282(86),266(100),250(36).

10-[[3-[4-(2-Hydroxyethyl)-1-piperazinyl][1,1,3,3-$^2H_4$]propyl]]-2-trifluoromethyl-10*H*-phenothiazine (13). A mixture of the labelled bromide 12 (1.085 g, 2.8 mmol) and 2-hydroxyethylpiperazine (0.718 g, 5.5 mmol) in 2-butanone (15 mL) was heated at reflux for 5 h. After cooling and removal of the solvent in vacuo, the residue was passed through a silica column (chloroform eluent) to give 1.181 g (89%) of a yellow oil. The resulting oil was dissolved in anhydrous ether, treated with ethereal HCl, and the solid which separated was recrystallised from absolute ethanol to afford the dihydrochloride salt of 13, mp 225-226°. ^{1}HNMR(free base,$CDCl_3$): δ1.90(s,2H,$C\underline{H}_2$-C^2H_2),2.30-2.70(m,10H, piperazine $C\underline{H}_2$ and $C\underline{H}_2$-piperazine),3.70(t,2H,$C\underline{H}_2$-O),3.80(broad s,1H,O$\underline{H}$), 6.60-7.20(m,7H,aromatic H); EIMS:m/z 441($M^{+\cdot}$,38),410(27),282 (100),266(13),250(13), 175(12),145(43),116(16),100 (19),98(18),73(17).

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