SYNTHESIS OF DEUTERIUM LABELLED TRIFLUOPERAZINE

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SUMMARY

Procedures for the preparation of trifluoperazine with two, four and six deuterium atoms are described. Deuterium was introduced in the propylpiperazine side chain by treatment of the appropriate amide with lithium aluminium deuteride. The isotopic purity of the products was greater than 96.2%.

Key Words : Trifluoperazine, deuterium labelling

INTRODUCTION

The quantitation of phenothiazine tranquilizers in the plasma of patients under treatment with these agents is difficult, because of the low levels encountered and their notorious instability in all stages of handling (1). The analysis of the more potent piperazine type phenothiazines, such as trifluoperazine, is particularly difficult because of the extremely low plasma levels encountered. We have recently reported a sensitive radioimmunoassay method for trifluoperazine; and it is necessary to verify such biological procedures by a chemical method (2). Gas chromatography-mass spectrometry (GLC-MS) is one of the few methods which has the necessary sensitivity and specificity for this comparison. Stable isotope analogues of trifluoperazine are needed as true internal standards for obtaining the required sensitivity on GLC-MS, as well as for subsequent pharmacokinetic studies. Generally these studies will need one or two other labelled standards for administration to human volunteers by one or two routes.

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The propylpiperazine side chain was chosen as the most suitable labelling site since it is generally not lost during metabolic processes in the body, and offers adequate variation in the number of labelled atoms. In this paper we describe the synthesis of trifluoperazine with two, four and six deuterium atoms in its propylpiperazine side chain.

DISCUSSION

In the case of phenothiazines compounds are known with a deuterium label in the propyl side chain (3,4), but a deuterium labelled piperazine ring in such compounds has not been reported. The piperazinones appeared suitable precursors for the introduction of a deuterium label in the piperazine ring. Indeed 1-methyl-3,5-piperazinedione (1, Figure 1), synthesised by urea fusion of the commercially available N-methyliminodiacetic acid (5), on reduction with lithium aluminium deuteride led to 1-methyl(3,3,5,5-$^{2}H_{4}$)piperazine (2) as the hydrochloride in good yield.

For the introduction of this key intermediate (2) into the trifluoperazine ring system, 3-[10-(2-trifluoromethylphenothiazinyl)]propionyl chloride (6) appeared attractive. Firstly, relatively mild conditions are involved in the formation and reduction of amides, and secondly this presents a facile way to introduce two further deuterium atoms. The necessary acid chloride (6), an unstable compound, was synthesised when required from the acid (5), a previously reported compound which was obtained as shown (3→5) (6,7).

The acid chloride (6) reacted with the unlabelled or labelled N-methylpiperazine in dry benzene to give 7 and 8 respectively; in the case of the tetradeuterated compound, the use of the dihydrochloride salt of 2 was necessary in this reaction, as the free base

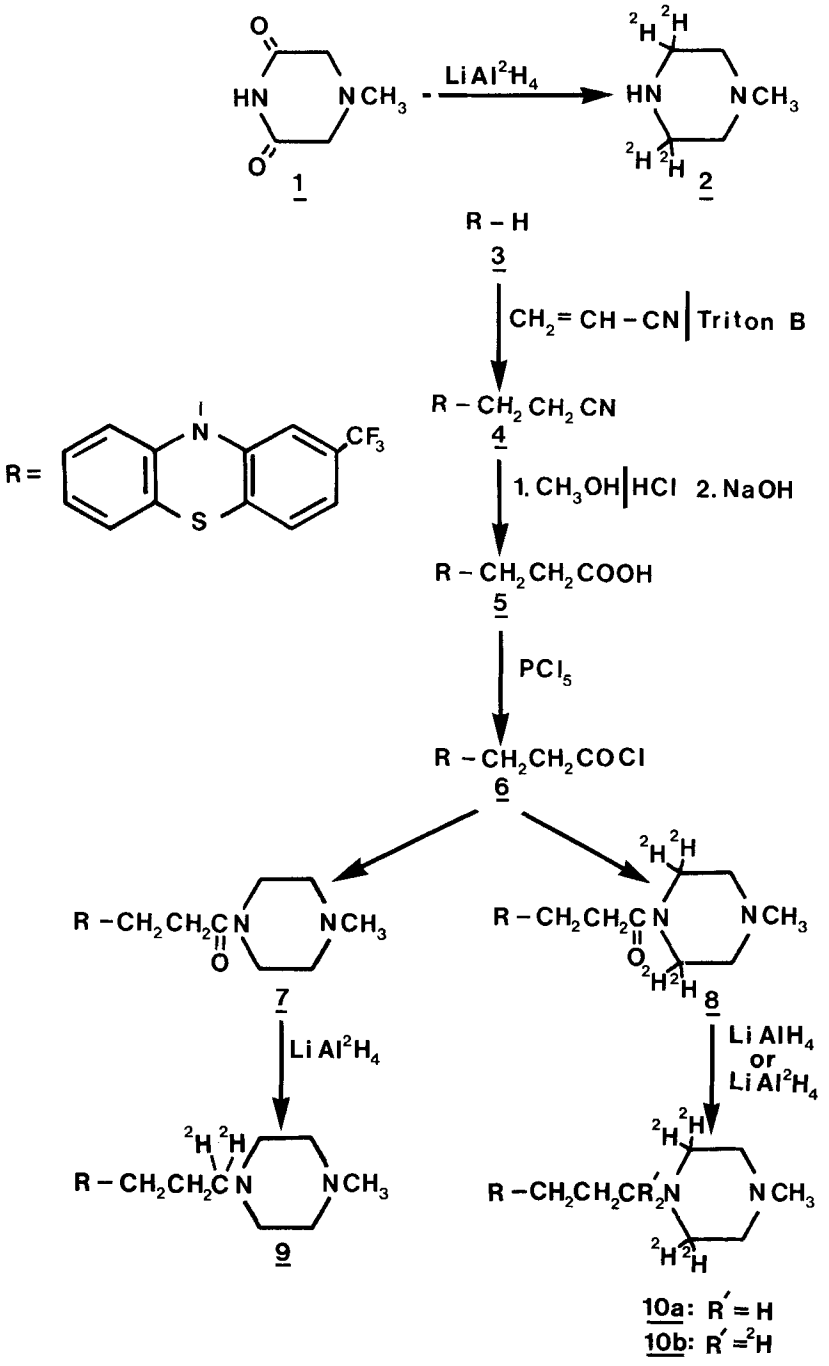
LiAl²H₄
1
2
R – H
3
CH₂ = CH – CN | Triton B
R – CH₂ CH₂ CN
4
1. CH₃OH | HCl 2. NaOH
R – CH₂CH₂COOH
5
PCl₅
R – CH₂CH₂COCl
6
R =
CF₃
7
8
LiAlH₄ or LiAl²H₄
9
10a: R′ = H
10b: R′ = ²H

FIGURE 1

piperazine could not be isolated in a dry condition. Reduction of the amides (7 and 8) with lithium aluminium hydride or deuteride gave the desired trifluoperazine unlabelled or with two, four and six deuterium atoms (9, 10a-b) in at least 55% yield. The isotopic purity of the labelled purified products was determined by MS using a single ion monitoring technique. The ratio for the molecular ions $^{2}Ho/^{2}Hn$ was shown to be 3.8, 1.3 and 0.3% for the di-(n=2), tetra-(n=4) and hexa-(n=6) deuterated trifluoperazine respectively. This purity is sufficient for use in GLC-MS and pharmacokinetic studies, and these results will be reported elsewhere.

EXPERIMENTAL

The melting points were determined on an electrothermal melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on pre-coated fluorescent silica gel sheets. Infrared (IR) spectra were recorded on a Perkin-Elmer 297 spectrometer. PMR spectra were determined with a Varian T-60 instrument; chemical shifts are expressed in δ units (parts per million) relative to TMS in $CDCl_3$ and DSS in D_2O. Electron impact mass spectra (EIMS) were obtained on a VG Micromass MM16F instrument at 70eV; relative intensity is noted in parentheses after each major fragment.

1-Methyl(3,3,5,5-$^{2}H_4$)piperazine dihydrochloride (2). The piperazinedione (1) (1.28 g, 10 mmol) (5) in dry THF (25 ml) was added dropwise over 1 hr. to a stirred suspension of lithium aluminium deuteride (1.26 g, 30 mmol) in dry THF. The resulting mixture was then refluxed for 4 hr., and subsequently cooled in ice and cautiously treated successively with moist ether (25 ml) and water (2 ml). The inorganic material was filtered off and extracted with ether in a Soxhlet apparatus. The combined ether extracts were treated with HCl in ether and evaporated to dryness under vacuum

with the aid of EtOH. Treatment with charcoal and crystallization from EtOH gave the piperazine (2) (1.24 g, 70%), m.p. 241.5-243°C as pale white crystals. A mixed m.p. with the authentic undeuterated salt was not depressed; PMR(D_2O) δ 3.03(S,3H,N-CH_3),3.66(S,4H, piperazine 2,6 methylene H); EIMS : 104($M^{+\cdot}$)(39),58(100),43(38), 42(21).

10-[3-(4-Methyl-1-piperazinyl)-3-oxopropyl]-2-trifluoromethyl-10*H*-phenothiazine (7). To a suspension of 10-(2-carboxyethyl-2-trifluoromethyl-10*H*-phenothiazine (5)(6,7) (1.017 g, 3 mmol) in dry benzene (10 ml) at 5°C was added with stirring phosphorus pentachloride (728 mg, 3.5 mmol) in dry benzene (5 ml) over a period of 1 hr. The mixture was allowed to stir for an additional 1 hr. during which time the pink colour disappeared. The solvent was removed under vacuum at 30-40°C and the oily residue treated with petroleum ether (10 ml) and filtered to yield 880 mg (82%) of the acid chloride (6), m.p. 62-64°C. The crude product was immediately used in the next stage of synthesis.

The acid chloride (6) (716 mg, 2 mmol) in dry benzene (5 ml) was added dropwise to a stirred solution of 1-methylpiperazine (220 mg, 2.2 mmol) in dry benzene (5 ml) at 5°C. The mixture was stirred for a further 4 hr. at room temperature and subsequently with 10% NaOH (5 ml) for 5 min. The organic layer was separated and washed successively with 10% NaOH and water. The benzene layer was dried ($MgSO_4$), filtered and evaporated to leave a yellow oil, which on passing through a neutral alumina column with benzene gave 7 as a colourless viscous oil (790 mg, 94%); TLC : Rf(95 C_6H_6 : 5 MeOH)0.44; IR($CHCl_3$) : 1620 cm^{-1}(NCO I); PMR($CDCl_3$) : δ 2.40(m, 7H,piperazine 3,5 methylene H and N-CH_3),2.80(t,2H,CH_2-CH_2-CO), 3.57(m,4H,piperazine 2,6 methylene H),4.33(t,2H,phenothiazine N-CH_2-),6.8-7.5(m,7H,aromatic H); EIMS : 421($M^{+\cdot}$)(100),280(43),

266(43),248(31),155(31),70(24),56(24).

10-[[3-[4-Methyl-1-(2,2,6,6-$^2H_4$)piperazinyl]-3-oxopropyl]]-2-trifluoromethyl-10*H*-phenothiazine (8). This was prepared from 5 by modification of the method described above for 7 : The hydrochloride salt of the labelled piperazine (2) was initially treated with anhydrous Na_2CO_3 in benzene under reflux until the evolution of CO_2 ceased. This mixture was subsequently treated with the acid chloride (6) as previously described. The product (8) was obtained (90% yield) as a colourless viscous oil : TLC and IR as for 8; PMR ($CDCl_3$) δ 2.38(m,7H,piperazine 3,5 methylene H and N-CH_3),2.80(t, 2H,-CH_2CO),4.33(t,2H,phenothiazine N-CH_2-),6.8-7.5(m,7H,aromatic H); EIMS : 425($M^{+\cdot}$)(100),280(52),266(40),248(26),159(69),72(40),57(35).

10-[3-(4-Methyl-1-piperazinyl)(3,3-$^2H_2$)propyl]-2-trifluoromethyl-10*H*-phenothiazine dihydrochloride (9). The amide (7) (421 mg, 1 mmol) in dry ether (5 ml) was added dropwise over 1 hr. to a stirred suspension of lithium aluminium deuteride (42 mg, 1 mmol) in dry ether (5 ml) at 0°C. After 30 min. reflux, water (0.5 ml), 15N NaOH (0.5 ml) and water (0.5 ml) were successively added. The ether layer was filtered off and the inorganic material was placed in the thimble of a Soxhlet apparatus and extracted with ether. The combined ether extracts were extracted with 10% HCl (5 ml x 4). The acid extract was washed with ether, the pH adjusted to 8.0 with Na_2CO_3, extracted with ether, and the combined ether extracts dried ($MgSO_4$) and filtered. Dry HCl in ether was added to the filtrate, and the solid which separated was recrystallised from EtOH to yield 265 mg (55%) of the dihydrochloride salt of trifluoperazine-d_2 (9), m.p. 241-243°C (lit.(8) unlabelled m.p. 242-243°C). A mixed melting point with the authentic undeuterated sample, prepared by the same route with lithium aluminium hydride or from a commercial source, was not depressed; TLC : Rf(100 MeOH : 20 H_2O : 3 NH_4OCOCH_3)

0.68; PMR(Free base, $CDCl_3$) : δ 1.90(t,2H,-$C\underline{H}_2CD_2$),2.20-2.56(m, 11H,piperazine methylene H and N-$C\underline{H}_3$),3.94(t,2H,phenothiazine N-$C\underline{H}_2$-),6.70-7.23(m,7H,aromatic H); EIMS : 409($M^{+}\cdot$)(51),308(13), 280(12),266(20),248(16),143(32),129(22),115(100),72(35),70(28), 56(10),43(25).

10-[[3-[4-Methyl-1-(2,2,6,6-$^2H_4$)piperazinyl]propyl]]-2-trifluoromethyl-10*H*-phenothiazine dihydrochloride (10a).

Trifluoperazine-d_4 (10a) was prepared (60% yield) from 8 and lithium aluminium hydride using the method described above for 9 : m.p. and TLC as for 9; PMR(free base, $CDCl_3$) : δ 1.90(q,2H,CH_2-$C\underline{H}_2$-CH_2),2.20-2.64(m,9H,-$C\underline{H}_2$-piperazine, piperazine 3,5 methylene H and N-$C\underline{H}_3$),3.97(t,2H,phenothiazine N-$C\underline{H}_2$-),6.76-7.40(m,7H, aromatic H); EIMS : 411($M^{+}\cdot$)(72), 306(15),280(19),266(22),248(17), 145(37),131(30),117(100),72(35),58(17),43(33).

10-[[3-[4-Methyl-1-(2,2,6,6-$^2H_4$)piperazinyl](3,3-$^2H_2$)propyl]]-2-trifluoromethyl-10*H*-phenothiazine dihydrochloride (10b).

Trifluoperazine-d_6 (10b) was prepared (56% yield) from 8 and lithium aluminium deuteride using the method described above for 9 : m.p. and TLC as for 9; PMR(free base, $CDCl_3$) : δ 1.90(t,2H,CH_2-$C\underline{H}_2$-CD_2),2.20-2.53(m,7H,piperazine 3,5 methylene H and N-$C\underline{H}_3$),3.97 (t,2H,phenothiazine N-$C\underline{H}_2$-),6.76-7.40(m,7H,aromatic H); EIMS : 413 ($M^{+}\cdot$)(20),308(13),280(13),266(22),248(17),147(35),133(25),119(100), 72(29),58(12),43(30).

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