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Synthesis of Deuterium-Labeled Prochlorperazine

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Abstract □ The propylpiperazine side chain of prochlorperazine was labeled with two, four, or six deuterium atoms by lithium aluminum deuteride reduction of the appropriate amide. The isotopic purity of the products after correcting for chlorine isotopes was >95.7%.

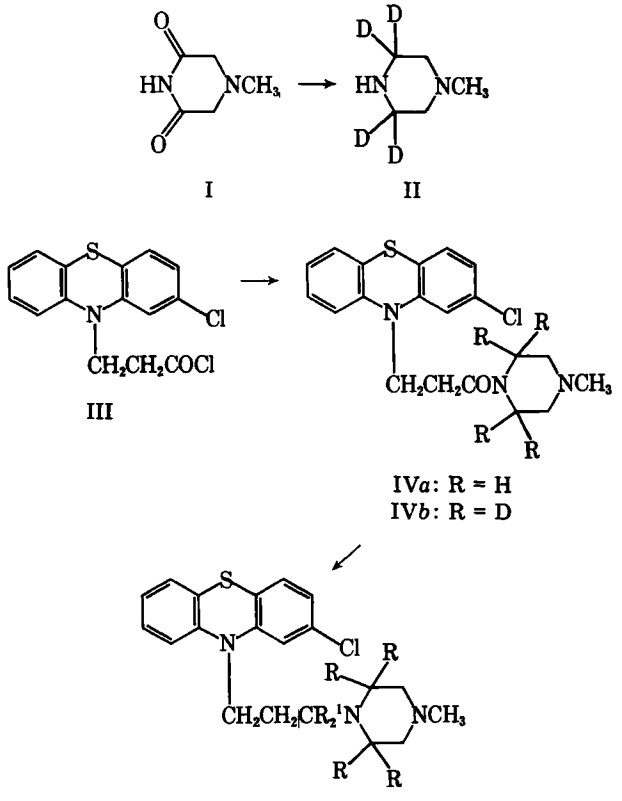
Keyphrases □ Prochlorperazine—deuterium-labeled synthesis □ Deuterium label—prochlorperazine synthesis

Prochlorperazine (V*a*), a piperazine-type phenothiazine, is primarily used as an antiemetic or antipsychotic. There are no literature reports that describe the usual plasma levels of this drug in patients under treatment, and, in fact, no suitable analytical methods have been described. The development of suitable analytical methods for the determination of the plasma concentrations of all piperazine-type phenothiazines has been slow, due to their instability in all stages of sample handling, as well as the extremely low plasma levels observed in the few studies involving humans.

BACKGROUND

The analytical procedures which have met the stringent sensitivity requirements of subnanogram determinations of these piperazine-type phenothiazines are either radioimmunoassay (RIA) or GLC–MS procedures (1, 2). In the case of prochlorperazine, an RIA method, which is capable of quantitating 0.125 ng/ml using 200-μl plasma aliquots, has been developed recently[1]. Following single 5-mg oral doses of prochlorperazine mesylate in healthy volunteers, the peak plasma concentrations were determined by RIA to be between 1–2 ng/ml. To verify the specificity of this sensitive biological procedure, a specific and sensitive chemical method such as GLC–MS is required. A stable isotope analogue of prochlorperazine was needed as a true internal standard for obtaining the required sensitivity by the chemical procedure. In addition, the availability of two other deuterium-labeled prochlorperazine standards will allow reliable pharmacokinetic studies to be carried out with fewer volunteers and animals, by administering these analogues by one or two routes and analyzing the plasma concentrations by GLC–MS using selected ion monitoring. Such studies will allow definitive pharmacokinetics of prochlorperazine to be obtained with far fewer administrations in volunteers.

The propylpiperazine side chain was chosen as the most suitable labeling site, since normally only the *N*-methyl group is lost during metabolism. It also offers adequate variation in the number of labeled atoms. Recently, the synthesis of labeled trifluoperazine, the 2-trifluoromethyl analogue of prochlorperazine, with two, four, or six deuterium atoms in the propylpiperazine side chain was successfully achieved (3). Similarly, this paper describes the synthesis of prochlorperazine with two, four, or six deuterium atoms.



Scheme I

RESULTS AND DISCUSSION

The synthesis (Scheme I) of the key tetradeuterated intermediate, 1-methyl(3,3,5,5-$^2H_4$)piperazine (II), from the lithium aluminum deuteride reduction of 1-methyl-3,5-piperazinedione (I) was previously described (3). Subsequent treatment of the unlabeled or labeled *N*-methylpiperazine in dry benzene with 3-[10-(2-chlorophenothiazinyl)]-

[1] K. K. Midha, E. M. Hawes, G. Rauw, J. McVittie, G. McKay, J. K. Cooper, and H. U. Shetty, unpublished work.

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propionyl chloride (III) gave the desired amides (IVa and b). In the case of the labeled *N*-methylpiperazine, the free base could not be obtained in a dry condition, necessitating the use of the hydrochloride in this reaction accompanied by the addition of sodium carbonate. This choice of route, involving an amide intermediate, allowed for the possibility of introducing two additional deuterium atoms. Reduction of the amides with lithium aluminum hydride or deuteride gave the desired prochlorperazine (V) with two, four, or six deuterium atoms in ~55% yield. The isotopic purity of the labeled, purified products was determined by MS spectrometry using a single-ion monitoring technique. The ratio for the molecular ions (^{35}Cl) $^2H_0/^2H_n$ was determined to be 0.43, 0.78, and 0.30% for the di-(n = 2), tetra-(n = 4), and hexa-(n = 6)deuterated prochlorperazine, respectively. The isotopic purities (after correcting for chlorine isotopes) for $^2H_2$, $^2H_4$, and $^2H_6$ were 98.11, 95.77, and 96.16%, respectively. The $^2H_1$ contaminant in the $^2H_2$ isomer was 1.89%, $^2H_2$ and $^2H_3$ contaminants collectively represented 4.23% in $^2H_4$, and $^2H_5$ contaminant in the $^2H_6$ isomer was 3.84%. It is evident that this purity is sufficient for use in GLC–MS and pharmacokinetic studies. These results will be reported elsewhere.

EXPERIMENTAL[2]

2-Chloro-10*H*-phenothiazine-10-propionyl Chloride (III)—A solution of phosphorus pentachloride (1.66 g, 8 mmoles) in 10 ml of dry benzene was added with stirring over 1.5 hr to a stirred suspension of 2-chloro-10-(2-carboxyethyl)-10*H*-phenothiazine (2.14 g, 7 mmoles) (4) in 25 ml of dry benzene at 5°. The reaction was allowed to proceed for 1 hr at room temperature during which time the pink mixture became colorless. Removal of the solvent *in vacuo* at 30° gave an oily residue which, on treatment with petroleum ether (40–60°), gave the acid chloride (III) in a 90% yield, mp 115–116° [lit. (4) mp 114–116°]. The product was unstable at room temperature and was immediately used in the next stage of the synthesis.

2 - Chloro - 10 - [[3-[4-methyl-1-(2,2,6,6-$^2H_4$)piperazinyl]-3-oxopropyl]]-10*H*-phenothiazine (IV*b*)—A mixture of 1-methyl(3,3,5,5-$^2H_4$)piperazine dihydrochloride (II) (3) (0.78 g, 4.4 mmoles) sodium carbonate (1.0 g), and dry benzene (20 ml) was refluxed until the evolution of carbon dioxide ceased. The mixture was then cooled to 0° and a solution of the acid chloride (III) (1.3 g, 4 mmoles) in 10 ml of dry benzene was added with stirring. When the addition was complete, the cooling bath was removed, and the mixture was allowed to warm to room temperature with continued stirring. After 3 hr, water (10 ml) was added, and vigorous stirring continued for 15 min. The organic layer was separated and washed successively with 10% aqueous sodium hydroxide (3 × 5 ml) and water (10 ml). The benzene layer was dried ($MgSO_4$) and evaporated to leave a yellow oil, which was purified by elution from a neutral alumina oxide column using benzene to give IV*b* as a colorless viscous oil in an 80% yield. TLC: R_f 0.44 (benzene–methanol, 95:5); IR (film) 1640 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 2.34 (m, 7H, piperazine-3,5-methylene and NCH_3), 2.85 (t, 2H, CH_2CO, J = 7 Hz), 4.23 (t, 2H, phenothiazine-CH_2, J = 7 Hz), and 6.8–7.4 (m, 7H, aromatic); MS: m/z 391(M^+, 100%), 248(31), 246(83), 234(33), 232(78), 214(27), and 159(77).

[2] *Melting points* were determined with a Gallenkamp melting point apparatus and are uncorrected. All TLCs were performed using Eastman Chromatogram sheets, type 13254 (silica gel with fluorescent indicator); spots were observed under shortwave UV light. IR spectra were taken on a Perkin-Elmer 297 spectrophotometer. NMR spectra were determined on a Varian T-60 instrument with tetramethylsilane as internal reference. Low resolution electron impact mass spectra were recorded on a VG Micromass MM16F instrument at 70 eV. Lithium aluminum deuteride (>99% deuterium) was obtained from Merck Sharp and Dohme, Dorval, Quebec and all other chemicals from Aldrich Chemical Co., Montreal, Quebec.

2-Chloro-10-[3-(4-methyl-1-piperazinyl)(3,3-$^2H_2$)propyl]-10*H*-phenothiazine Dihydrochloride (V*b*)—A solution of 2-chloro-10-[3-(4-methyl-1-piperazinyl)-3-oxopropyl]-10*H*-phenothiazine (IV*a*) (0.39 g, 1 mmole), a previously reported (5) compound prepared in a manner similar to IV*b*, in 5 ml of dry ether was added dropwise over 1 hr to a stirred suspension of lithium aluminum deuteride (0.042 g, 1 mmole) in 5 ml of dry ether at 0°. The mixture was stirred for an additional 15 min, and after treatment with water (0.5 ml) and 20% aqueous sodium hydroxide (1 ml) the ether layer was decanted off. The inorganic material was mixed with sodium chloride (0.25 g), placed in the thimble of a Soxhlet apparatus, and extracted for 3 hr with ether. The combined ether fractions were extracted with 10% HCl (4 × 5 ml). The combined aqueous extracts were then washed with ether (3 × 5 ml) and the pH adjusted to 8.0 with saturated sodium carbonate solution. The product was then extracted with ether (4 × 10 ml), and the combined ether extracts dried ($MgSO_4$) and filtered. Dry hydrogen chloride in ether was added to the filtrate and the separated solid crystallized from ethanol to afford ($^2H_2$)-prochlorperazine (V*b*) as the dihydrochloride salt (0.25 g, 55%), mp 242–243°. Mixed melting points with the authentic nondeuterated samples (V*a*), prepared by the same route with lithium aluminum hydride or prepared from a commercial sample of prochlorperazine free base, were not depressed. TLC: R_f 0.55 (methanol–water–ammonium acetate, 100:20:3); NMR (free base, $CDCl_3$): δ 1.85 (t, 2H, CH_2CD_2, J = 6.5 Hz), 2.24 (s, 3H, NCH_3), 2.40 (s, 8H, piperazine methylene), 3.84 (t, 2H, phenothiazine-CH_2, J = 6.5 Hz), and 6.72–7.20 (m, 7H, aromatic); MS: m/z 375(M^+, 47%), 274(7), 246(8), 232(16), 143(33), and 115(100).

2-Chloro-10-[[3-[4-methyl-1-(2,2,6,6-$^2H_4$)piperazinyl]-propyl]]-10*H*-phenothiazine Dihydrochloride (V*c*)—($^2H_4$)-Prochlorperazine (V*c*) was prepared (55%) from IV*b* and lithium aluminum hydride using the method described above for V*b*: mp and TLC as for V*b*. NMR (free base, $CDCl_3$): δ 1.94 (m, 2H, propyl central CH_2), 2.30–2.66 (m, 9H, CH_2-piperazine, piperazine-3,5-methylene, and NCH_3), 3.88 (t, 2H, phenothiazine-CH_2, J = 6.5 Hz), and 6.60–7.18 (m, 7H, aromatic); MS: m/z 377(M^+, 69%), 273(14), 246(11), 232(13), 145(40), and 117(100).

2-Chloro-10-[[3-[4-methyl-1-(2,2,6,6-$^2H_4$)piperazinyl](3,3-$^2H_2$)propyl]]-10*H*-phenothiazine Dihydrochloride (V*d*)—($^2H_6$)-Prochlorperazine (V*d*) was prepared (55% yield) from IV*b* and lithium aluminum deuteride using the method described above for V*b*: mp and TLC as for V*b*. NMR (free base, $CDCl_3$): δ 1.85 (t, 2H, CH_2CD_2, J = 6.5 Hz), 2.20 (s, 3H, NCH_3), 2.37 (s, 4H, piperazine-3,5-methylene), 3.85 (t, 2H, phenothiazine-CH_2, J = 6.5 Hz), and 6.62–7.15 (m, 7H, aromatic); MS: m/z 379(M^+, 49%), 276(10), 274(10), 246(8), 232(14), 214(8), 147(48), and 119(100).

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