SYNTHESIS OF CLOMIPRAMINE-d_8

Naba K. Chaudhuri*, Ming-Sang Sung and Bohdan Markus

Research Department, Pharmaceuticals Division
CIBA-GEIGY Corporation
Ardsley, N. Y. 10502, U.S.A.

SUMMARY

The synthesis of deuterium labelled clomipramine which is an antidepressant drug is described. Eight deuterium atoms have been incorporated specifically into the nonaromatic part of the molecule -- six atoms at 1, 2, and 3 positions of the dimethylaminopropyl side chain and two atoms at the 10 and 11 positions of the molecule. 1,1,2,2,3,3-Hexadeutero-3-dimethylaminopropyl chloride has been synthesized for this purpose and used for the construction of the labelled side chain.

KEYWORDS: Clomipramine-d_8, 1,1,2,2,3,3-Hexadeutero-3-dimethylaminopropyl chloride, 2-Bromoethanol-d_4.

INTRODUCTION

The hydrochloride salt of clomipramine (3-chloro-5-[3-dimethylaminopropyl]-10,11-dihydro-5H-dibenz[b,f]azepine) (1) is a widely used anti-depressant drug. A stable isotope labelled variant of this drug was needed in our laboratory to study relative bioavailability of different formulations in man by the application of a gas chromatography mass spectrometry (GC-MS) method with selected ion

*Author to whom correspondence should be addressed.

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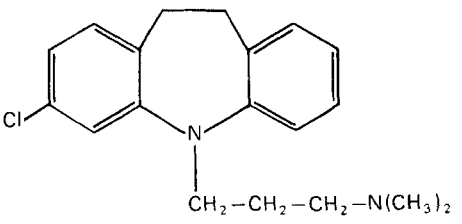
monitoring (1). The ion chosen for monitoring in this method was at m/e 254 which may be represented by structure 2. For optimum sensitivity, it was desirable that the labelled drug has a molecular weight of at least 3 mass units higher than the unlabelled drug. Recently, we published a method for



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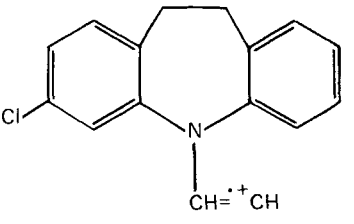

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the synthesis of tetradeuterated imipramine having all the four deuterium ions at 10, 11 positions (2). This method could not be applied for the synthesis of clomipramine, tetradeuterated at 10, 11 positions because clomipramine is unsymmetrically substituted with a chlorine atom at one of the benzene rings. Therefore, we synthesized an octadeuterated clomipramine (14) having six deuterium atoms in the side chain and two deuterium atoms at 10 and 11 positions.

METHODS AND RESULTS

The synthesis of octadeuterated clomipramine (14) consists of preparing the two molecular components 9 (Scheme 1) and 13 (Scheme 2) which were then

condensed in the presence of a strong base to give 14. The side chain component, 1,1,2,2,3,3-hexadeutero-3-dimethylaminopropyl chloride (9), was synthesized in six steps (Scheme 1) from ethylene glycol-d_4 (3) in an overall yield of about 30%.

Scheme 1

$$\underset{\underline{3}}{HO\text{-}CD_2\text{-}CD_2\text{-}OH} \longrightarrow \underset{\underline{4}}{Br\text{-}CD_2\text{-}CD_2\text{-}OH} \longrightarrow \underset{\underline{5}}{NC\text{-}CD_2\text{-}CD_2\text{-}OD}$$

$$\longrightarrow \underset{\underline{6}}{D_2N\text{-}CD_2\text{-}CD_2\text{-}CD_2\text{-}OD} \longrightarrow \underset{\underline{7}}{(CH_3)_2N\text{-}CD_2\text{-}CD_2\text{-}CD_2\text{-}OH}$$

$$\longrightarrow \underset{\underline{8}}{Cl\text{-}CD_2\text{-}CD_2\text{-}CD_2\text{-}N(CH_3)_2\cdot HCl} \longrightarrow \underset{\underline{9}}{Cl\text{-}CD_2\text{-}CD_2\text{-}CD_2\text{-}N(CH_3)_2}$$

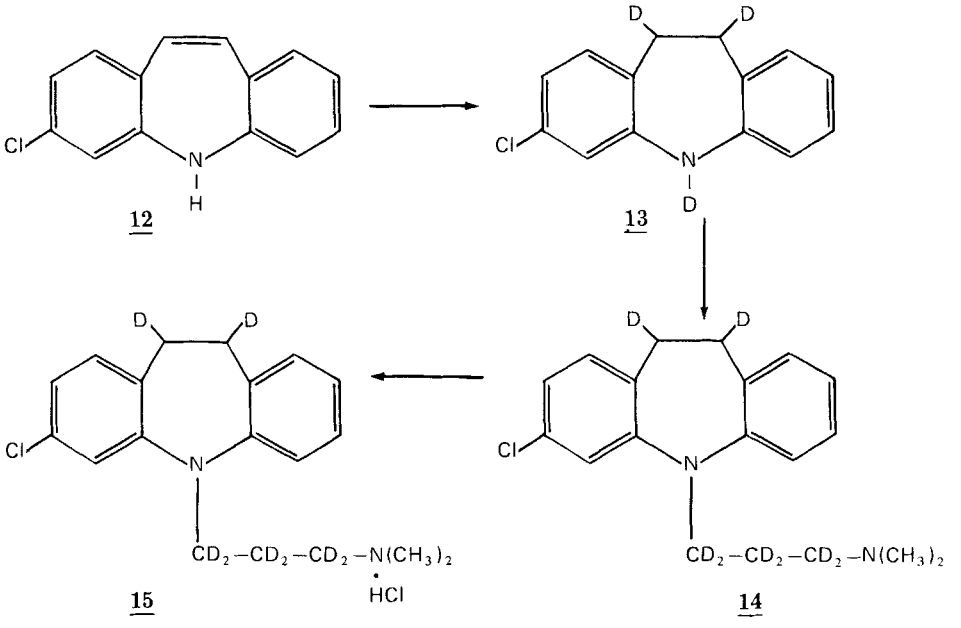
Ethylene glycol-d_4 (3) was heated with one equivalent of phosphorous tribromide to give 2-bromoethanol (4) in 76% yield along with a small amount of ethylene dibromide which was separated by distillation. The reaction of 4 with potassium cyanide in deuteroethanol (C_2H_5OD) and deuterium oxide gave ethylene cyanohydrin-d_4 (5) in 80-85% yield. When ordinary ethanol and water were used as solvent, the deuterium atoms attached to the carbon atom alpha to the nitrile group of 5 were lost through base catalyzed exchange by the solvent protons. It is important that the basic reaction mixture is neutralized before the cyanohydrin 5 is isolated by distillation, otherwise considerable polymer-

$$\underline{5} \xrightarrow{\text{Base}} \underset{\underline{10}}{NC\text{-}\overline{C}D\text{-}CD_2OH} \longrightarrow \underset{\underline{11}}{NC\text{-}CD = CD_2}$$

ization takes place due to the formation of acrylonitrile (11) by the base catalyzed dehydration of 5 via 10. Reduction of 5 with lithium aluminum deuteride followed by decomposition with deuterium oxide gave the aminoalcohol 6 which was then methylated by means of Eschweiler-Clarke reaction (3) using formaldehyde and formic acid to give hexadeuterated 3-dimethylaminopropyl alcohol (7). The reaction of 7 with thionyl chloride gave the hydrochloride 8 which on base treatment generated hexadeuterated 3-dimethylaminopropyl chloride (9).

The tricyclic component 13 was prepared by catalytic reduction of the 10,11-double bond of 3-chloro-5H-dibenz[b,f]azepine (12) with deuterium after exchanging the NH proton with deuterium. If the NH proton is not exchanged before reduction, it exchanges with deuterium during catalytic reduction and becomes incorporated at the 10 and 11 positions along with deuterium atoms.

Scheme 2



Compound 13 was condensed with freshly prepared hexadeuterated 3-dimethylaminopropyl chloride (9) in the presence of lithium amide to give octadeuterated clomipramine 14 which was then converted to its hydrochloride salt 15 for bioavailability studies. The mass spectrum of 15 showed a fragment ion at m/e 258 which is four mass units higher than the fragment ion 2 derived from unlabelled clomipramine.

3-Dimethylaminopropyl chloride is an important synthetic intermediate which has been used for the synthesis of a large number of drugs like imipramine, chlorpromazine, amitryptiline etc. The synthesis of its hexadeuterated analog 9, thus provides a method for the preparation of these drugs labelled with deuterium atoms.

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectral data are reported in parts per million (ppm) deshielded with respect to tetramethylsilane. NMR spectra at 90 MHz were recorded on a Varian EM-390 spectrometer and the mass spectra were obtained on a Finnigan 3300 instrument. Thin layer chromatography (tlc) was carried out on silica gel 60 F254 plates of 0.5 mm layer thickness. Ethylene glycol -d_4 was obtained from KOR ISOTOPES of Cambridge, Massachusetts, U.S.A.

2-Bromoethanol-d_4 (4). To 25 g of ethylene glycol was slowly added 13 ml (37 g) of phosphorous tribromide and the mixture was then heated at 90° for 6 hours. The product was isolated by distillation through a 2" Vigreux column. The first fraction (8 g) distilling at 55-60°/25 mm had infrared bands and

NMR peaks identical to those of an authentic sample of 1,2-dibromoethane. The second fraction (36 g), after redistillation at 60-65°/25 mm had infrared bands and NMR peaks identical to those of authentic 2-bromoethanol. The above reaction was repeated using 26 g of ethylene glycol-d_4 and 13 ml of phosphorous tribromide under the same conditions to give 9 g of 1, 2-dibromoethane-d_4 and 38 g (76% yield) of 2-bromoethanol-d_4.

Ethylene Cyanohydrin-d_5 (5). To a solution of 38 g of the above 2-bromoethanol-d_4 and 100 ml of deuteroethanol (C_2H_5OD) was added a solution of 21 g of potassium cyanide in 30 ml of deuterium oxide and the solution was refluxed for 6 hours. The reaction mixture was then cooled in ice bath and filtered to remove potassium bromide. The filtrate was concentrated by removing ethanol under reduced pressure at 40°. The residual solution was neutralized by addition of DCl/D_2O and diluted with acetone. The precipitate of potassium bromide was removed by filtration and then washed with acetone. The filtrate was freed of acetone by distillation under reduced pressure in a rotary evaporator. The residue was then distilled and the fraction distilling at 83-85°/1.5 mm was collected; yield-17.5 g (about 80%).

Anal. Calcd. for C_3D_5NO: C, 47.32%; N, 18.40%. Found: C, 46.99%; N, 18.35%.

3-Dimethylaminopropanol-d_6 (7). To a solution of 12.8 g of the above cyanohydrin 5 in 150 ml of dry tetrahydrofuran cooled to -20° was dropwise added a solution of 10 g of lithium aluminum tetradeuteride in 200 ml of tetrahydrofuran with continued cooling. After the addition was completed, the reaction mixture was brought to room temp. and then heated under reflux for 8 hours. The mixture was cooled and decomposed by the addition of 10 ml of D_2O, 10 ml of 15% NaOD

followed by 30 ml of D_2O. The solid was removed by filtration and washed three times with tetrahydrofuran. The filtrate and washings were combined and then evaporated under reduced pressure in a rotary evaporator. To the residue was then added 50 ml of 95% formic acid with cooling followed by 50 ml of 37% formaldehyde solution and the solution was heated under reflux for 12 hours. Conc. hydrochloric acid (40 ml) was added to the above solution which was then evaporated to dryness in a rotary evaporator under reduced pressure. The residue was treated with excess of 50% aq. sodium hydroxide solution and the product extracted four times with ether. The ether solution was dried with anhydrous magnesium sulfate, filtered and evaporated to dryness. The residue was distilled in vacuo and the fraction distilling at 95-100°/15 mm was collected; yield 11 g (60% in two steps from the nitrile 5).

Anal. Calcd. for $C_5H_7D_6NO$: C, 54.96%; N, 12.82%. Found:
C, 54.73%; N, 13.19%.

NMR ($CDCl_3$): 2.2 [s, 6H, N (CH_3)$_2$]; 4.7 (1H, OH)

5,10,11-Trideutero-3-chloro-10,11,-dihydro-5H-dibenz[b,f]azepine (13). To a warm solution of 50 g of 3-chloro-5H-dibenz[b,f]azepine (12) in toluene was added 10 g of sodamide with stirring. The mixture was then heated at 60° for 3 hours and quenched with D_2O. The toluene solution was cooled and filtered. The filtered solid was suspended in 250 ml of ethyl acetate and 2 g of 10% palladium on charcoal catalyst was added to it. The reaction bottle was then shaken in an atmosphere of deuterium in a Paar hydrogenation apparatus at 35 lbs/sq inch for 2 hours when the uptake of deuterium ceased. The ethyl acetate solution was filtered to remove the catalyst and then concentrated to a small

volume. Crystallization set in on cooling. The crystals were separated by filtration; yield 50 g (98%); m.p. 86-88°. The reported (4) m.p. of 3-chloro-10,11-dihydro-5H-dibenz[b,f]azepine is 87-89°.

1,1,2,2,3,3-Hexadeutero-3-dimethylaminopropyl chloride hydrochloride (8). To a solution of 11 g of 7 in 50 ml of chloroform was slowly added 35 ml of thionyl chloride and the solution was then heated under reflux for 2 hours. The solvent and excess of thionyl chloride were removed by distillation under reduced pressure in a rotary evaporator to give a white solid. A small amount of the solid was dried in a vacuum dessicator. It had a m.p. of 140-42°. The reported (5) m.p. of 3-dimethylaminopropyl chloride hydrochloride is 142°. The above hydrochloride 8 was dissolved in 10 ml of water, basified with 6N sodium hydroxide solution and extracted three times with ether. The ether extract was dried with anhydrous magnesium sulfate, filtered and evaporated in a rotary evaporator and the crude oil (11 g) was immediately used in the next step.

3-Chloro-10,11-dideutero-5-(3-dimethylamino-1,1,2,2,3,3-hexadeuteropropyl)-10,11-dihydro-5H-dibenz[b,f]azepine (14). To a suspension of 3.8 g of lithium amide in 20 ml of toluene was added 20 g of 13 in 60 ml of toluene and the mixture was heated with stirring at 80-90° for 2 hours. The mixture was then brought to room temp, a solution of 11 g of 9 in 60 ml of toluene was added to it and then refluxed overnight. After cooling to room temp, the reaction mixture was decomposed by the addition of 50 ml of ice-water. The toluene layer was separated from the aqueous layer, dried with anhydrous magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure

give an oily residue which was purified by salt formation with oxalic acid. To a solution of the above oil in 200 ml of ether was added an ethanolic solution of 8 g of oxalic acid. The salt was removed by filtration and crystallized from ethanol (m.p. 167-69°). Recrystallization gave 18 g of the oxalate salt (m.p. 170-72°). The oxalate salt was dissolved in water and basified with sodium hydroxide and extracted with ether. The ether extract was dried with anhydrous magnesium sulfate and filtered. The filtrate was treated with a solution of hydrogen chloride in ether and the precipitate was twice crystallized from acetone, m.p. 190-91°. The reported (6) m.p. of clomipramine hydrochloride is 189-90°; yield 15.8 g (51%).

Anal. Calcd. for $C_{19}H_{16}D_8Cl_2N_2$: C, 63.50; N, 7.80. Found: C, 63.70; N, 7.85.

NMR ($CDCl_3$); 2.6 [$N(CH_3)_2$], 3.1 (-CHD), 6.95 and 7.1-7.2 (Aromatic).

Mass Spectrum: m/e 322 (M^+ - HCl)

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