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SYNTHESIS OF DEUTERIUM-LABELLED VILOXAZINE

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SUMMARY: The synthesis of deuterium-labelled viloxazine with high isotopic purity is described. The synthetic procedures employ alkylation of 2-(benzyloxy)phenol with [$^2H_5$]ethyl iodide for the introduction of deuterium. Catalytic removal of the benzyl group of the deuterated product followed by reaction with epichlorohydrin afforded 1,2-epoxy-3-(2'-pentadeuteroethoxyphenoxy)propane. Addition of 2-aminoethyl hydrogen sulphate to the epoxide and subsequent ring formation into a morpholine derivative produced the desired [$^2H_5$]viloxazine.

Key words: viloxazine, antidepressant, deuterium labelling, alkylation with [$^2H_5$]ethyl iodide

INTRODUCTION

Viloxazine, 2-[(2'-ethoxyphenoxy)methyl]morpholine, is a chemically novel antidepressant and one of the so-called "second generation antidepressants" (1,2). This drug is administered as the racemate and it has been shown that the optical isomers elicit differences in pharmacological potency (3,4). Therefore, pharmacokinetic studies of viloxazine should involve measurement of each enantiomer.

As the first stage in the development of gas chromatography-mass spectrometry (GC-MS) with selected ion monitoring for the determination of viloxazine in plasma and other body fluids, we have synthesized a deuterium labelled analogue for use as an internal standard. The preparation of [$^2H_5$]viloxazine described in this paper has the merit of simplicity and the product is of high isotopic purity.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on Merck DC-Fertigplatten Kieselgel 60 F_{254}. High performance liquid chromatography (HPLC)

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was performed on a Hitachi 638-30 Liquid Chromatograph fitted with a variable-wavelength detector (monitored at 280 nm) using C.I.G. column (300 mm x 22 mm i.d., Kusano Kagaku, Ltd., Japan). The mobile phase was MeOH:CH_2Cl_2:n-hexane (1:3:6) and the flow rate 3 mL/min. ^1H NMR spectra were determined on Varian EM-390 90 MHz and Bruker AM-400 400 MHz spectrometers for solutions in $CDCl_3$ and CCl_4 (Me_4Si as an internal standard). Electron impact mass spectra (EIMS) were recorded on a Hitachi M-80 mass spectrometer and a Shimadzu QP 1000 gas chromatograph-mass spectrometer at 70 eV. Pentadeuteroethyl iodide (isotopic purity, 99%) was purchased from ICN Biomedicals, Inc. (Cambridge, MA, USA). All chemicals and reagents were of analytical reagent grade and were used without further purification.

1-Benzyloxy-2-[$^2H_5$]ethoxybenzene (2)

To a suspension of 2-(benzyloxy)phenol (1, 1.1 g, 5.7 mmol) and K_2CO_3 (1.4 g, 10 mmol) in DMF (2 mL) was added pentadeuteroethyl iodide (2.0 g, 12.1 mmol). The reaction mixture was then stirred at room temperature for 17.5 h (5). The reaction mixture was extracted with CH_2Cl_2 (5 x 5 mL) and the combined extracts were washed with H_2O (6 x 5 mL). After drying over anhydrous Na_2SO_4, the solution was evaporated to dryness under reduced pressure. The resulting brownish oily product (1.1 g, 79%) showed a single spot on TLC (R_f: 0.51, EtOAc:n-hexane; 3:7 as developing solvent). δ_H(90 MHz, CCl_4) 5.0 (2 H, s, -O-CH_2- of benzyl), 6.8 (4H, s, ArH in catechol) and 7.3 (5 H, m, ArH in benzyl).

2-[$^2H_5$]Ethoxyphenol (3)

To a suspension of 2 (1 g, 4.4 mmol) in EtOH (50 mL) was added 10% Pd-C (0.8 g). The solution was stirred under a hydrogen atmosphere for 2.5 h at room temperature. The uptake of hydrogen was ca. 65 mL (theoretical volume, 49 mL). After the catalyst was removed by filtration, the filtrate was evaporated to dryness under reduced pressure to give an oily product (0.5 g, 80%), which showed a single spot on TLC (R_f: 0.43, EtOAc:n-hexane; 3:7 as developing solvent). δ_H(90 MHz, CCl_4) 5.4 (1 H, s, -OH) and 6.7 (4 H, m, ArH in catechol).

1,2-Epoxy-3-(2'-[$^2H_5$]ethoxyphenoxy)propane (4)

To a solution of the labelled 2-(ethoxy)phenol 3 (0.5 g, 3.5 mmol) in 5M NaOH was added epichlorohydrin (0.6 g, 5.3 mmol) dropwise. After stirring at 20 °C for 18 h, the reaction mixture was extracted with CH_2Cl_2 (5 x 5 mL). The combined extracts were

washed with H_2O (5 x 5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded a crude oily material. After purification by preparative TLC (R_f: 0.52, EtOAc:n-hexane; 8:2 as developing solvent), the pure product 4 was obtained. δ_H(90 MHz, CCl_4) 2.5-2.8 (2 H, m, $-CH_2-$ of ethylene oxide), 3.0-3.2 (1 H, m, -CH-), 3.9-4.2 (2 H, m, $-O-CH_2-$) and 6.7 (4 H, s, ArH).

2-[(2'-[$^2H_5$]Ethoxyphenoxy)methyl]morpholine (5)

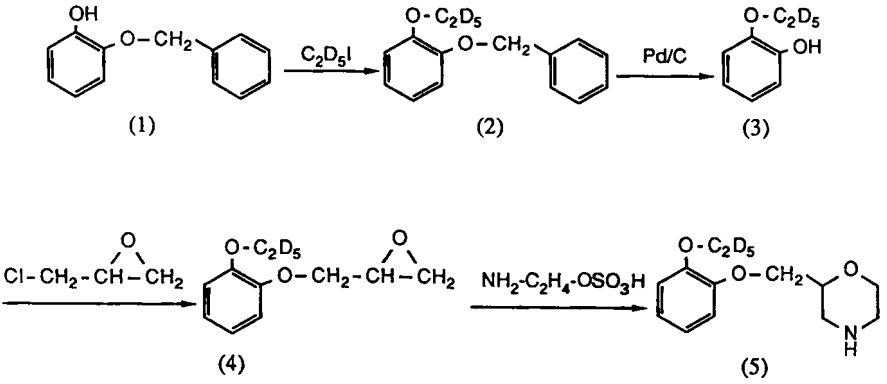
To a solution of the epoxide 4 (0.7 g, 3.6 mmol) in EtOH (14 mL) were added 2-aminoethyl hydrogen sulphate (2.5 g, 17.7 mmol) and 5M NaOH (7 mL). The reaction mixture was then stirred at 60 °C for 18 h (6). After evaporating the solvent at 40 °C under reduced pressure, H_2O (10 mL) was added to the residue and the aqueous solution was extracted with ether (3 x 10 mL). The combined extracts were concentrated to ca. 2 mL and acidified to pH 3 with 0.5M HCl. The solution was extracted with $CHCl_3$ (5 x 5 mL), the extract being discarded. The aqueous layer was adjusted to pH ca. 9 with 0.5M NaOH and extracted with $CHCl_3$ (4 x 5 mL). The combined extracts were dried over anhydrous Na_2SO_4 and then evaporated to dryness under reduced pressure to give a crude oily product (0.25 g). Purification by TLC (R_f: 0.1-0.2, MeOH:$CHCl_3$; 1:9 as developing solvent) and HPLC resulted in the pure product 5 as an oil (135 mg, 10.3%). m.p. of the HCl salt 175-178 °C (lit. (6) 179-182 °C, nonlabelled 5 as a HCl salt). δ_H(400 MHz; $CDCl_3$) 1.50-2.00 (1 H, s, N-H), 2.73-2.79 and 2.89-2.96 (1 H, q and 1 H, q, C_5-H), 2.82-2.85 and 3.11-3.14 (1 H, q snd 1 H, q, C_3-H), 3.63-3.69 (1 H, m, C_6-H), 3.85-3.95 (3 H, m, C_2-H, C_6-H and -O-$\dot{C}$H-), 4.03-4.09 (1 H, q, -O-$\dot{C}$H-) and 6.87-6.94 (4 H, m, ArH). EIMS of labelled and nonlabelled 5: m/z 242 and 237 ($M^{+\bullet}$, relative intensity 30%), m/z 143 and 138 ($M^{+\bullet}$ - methylmorpholine moiety, relative intensity 70%), m/z 100 (methylmorpholine fragment, base peak) and m/z 56 (C_3H_6N fragment, relative intensity 70%).

RESULTS AND DISCUSSION

The synthetic procedures, presented in Scheme 1, employ a conventional alkylation of 2-(benzyloxy)phenol 1 with [$^2H_5$]-ethyl iodide in the presence of K_2CO_3 (5) for the introduction of deuterium. Catalytic removal of the benzyl group of the deuterated compound 2 produced 2-(pentadeuteroethoxy)phenol 3 which subsequently reacted with epichlorohydrin to afford 1,2-epoxy-3-(2'-pentadeuteroethoxyphenoxy)propane 4 (6). Nucleophilic addition of 2-aminoethyl hydrogen sulphate to the epoxide

and subsequent ring formation into a morpholine derivative gave the desired ^2H-labelled viloxazine 5 (6).

The incorporation of deuterium in synthetic intermediates and the desired product was assessed by ^1H NMR and MS analyses. ^1H NMR data for the intermediate 2 indicated that the signals at δ_H1.3-1.6 (3H, t, $-CH_3$) and δ_H 3.9-4.2 (2H, q, $-CH_2-$) observed for the non-labelled 2 disappeared completely in labelled 2.



Scheme 1

Similar observations were made when in turn the ^1H NMR spectrum of 3, 4, and 5 were compared with the respective spectrum of each nondeuterated compound. The MS spectrum of deuterated viloxazine 5 indicated, by comparison with the non-labelled analogue, that ions at m/z 242 ($M^{+\bullet}$) and 143 $(M-99)^+$ retaining the ethyl group are shifted by 5 mass units.

The isotopic purity of [$^2H_5$]viloxazine was determined by GC-MS analyses of the parent compound with selected ion monitoring of the $M^{+\bullet}$ ion at m/z 242. The percentage of deuterium incorporation in viloxazine was 95.6% for the $^2H_5$-species and 4.4% for the $^2H_4$-species, the deuterium content of [^2H] viloxazine being 99.1 atom% d. There was no indication of deuterium scrambling during the synthetic procedures as evidenced by the analyses of ^1H NMR and GC-MS. The deuterium label is stable under even strongly acidic or basic conditions and [$^2H_5$]-viloxazine obtained is suitable for use as an internal standard in the quantificaton of viloxazine in body fluids by GC-MS (K. Mamada et al., unpublished work).

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