THE SYNTHESIS OF DEUTERIUM LABELLED ANALOGUES OF A NOVEL ANTIDIARRHOEAL AGENT, 2-[3,3-Diphenyl-3-(2-methyl-1,3,4-oxadiazol-5-yl) propyl]-2-azabicyclo[2,2,2] octane

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SUMMARY

The synthesis of three deuterated analogues[d_4, d_6 and d_9] of the novel antidiarrhoeal agent 2-[3,3-diphenyl-3-(2-methyl-1,3,4-oxadiazol-5-yl) propyl]-2-azabicyclo[2,2,2]octane is described. The compounds prepared were of high isotopic purity and were used in metabolism and bioavailability studies.

Key Words: 2-[3,3-diphenyl-3-(2-methyl-1,3,4-oxadiazol-5-yl) propyl]-2-azabicyclo-[2,2,2]octane, deuterium, synthesis, isotopic purity.

INTRODUCTION

In order to study the absolute availability in animals and man of the novel antidiarrhoeal agent, 2-[3,3-diphenyl-3-(2-methyl-1,3,4-oxadiazol-5-yl) propyl]-2-azabicyclo[2,2,2]octane,[1] (Nufenoxole (R) G.D. Searle & Co. Ltd.) using the technique of co-administration of unlabelled drug and cold labelled drug, whilst using a further labelled analogue as an internal standard and carrier for the mass spectrometric assay;[2,3] the synthesis of the compound with four and six deuterium atoms was required. The unlabelled compound and the tetradeutero analogue, which was labelled at a metabolically inert position, were administered simultaneously by intravenous and oral routes. The nonadeutero analogue was used to establish

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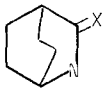
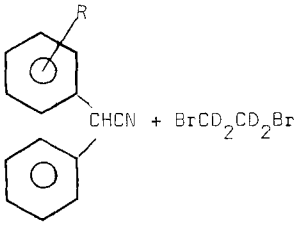
the fragmentation pathway for the compound observed using the electron impact ionisation mode in the mass spectrometer.[3]

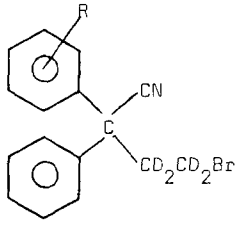


Ia, X = O
b, X = H_2
c, X = D_2

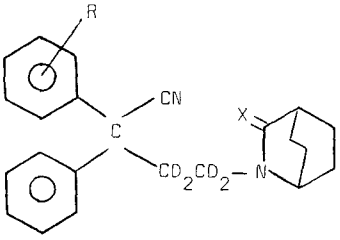
SCHEME A



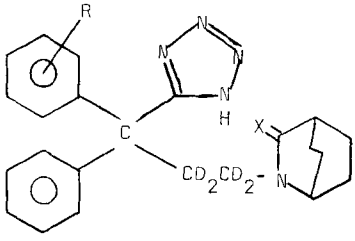
IIa, R = 5H
b, R = 5D



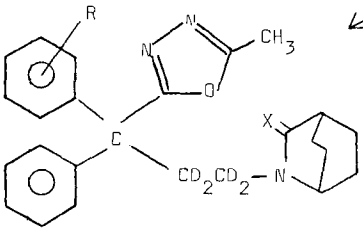
IIIa, R = 5H
b, R = 5D



IVa, R = 5H, X = H_2
b, R = 5H, X = D_2
c, R = 5D, X = H_2



Va, R = 5H, X = H_2
b, R = 5H, X = D_2
c, R = 5D, X = H_2



VIa, R = 5H, X = H_2
b, R = 5H, X = D_2
c, R = 5D, X = H_2

DISCUSSION

The synthetic route to the $[d_4]$-, $[d_6]$- and $[d_9]$ analogues is similar to that described for the unlabelled compound and is shown in Scheme A. For the synthesis of $[d_4]$ Nufenoxole, $[d_4]$ 1,2-dibromoethane was used to prepare the intermediate $[d_4]$ 4-bromo-2,2-diphenylbutyronitrile (IIIa). Condensation of (IIIa) with 2-azabicyclo $[2,2,2]$ octane (Ib) in the presence of aqueous potassium hydroxide gave the product (IVa) which was converted to the tetrazole (Va) using sodium azide in the presence of ammonium chloride and lithium chloride in dimethyl formamide as solvent at 120°C. The tetrazole (Va) was heated under reflux with a mixture of acetic anhydride and pyridine; after isolation the crude product was dissolved in benzene and passed through a short column of alumina. The solid obtained on concentration of the combined eluant was recrystallised from isopropanol to give $[d_4]$ Nufenoxole (VIa). The preparation of $[d_6]$ Nufenoxole (VIb) was achieved by using both $[d_4]$ 4-bromo-2, 2-diphenylbutyronitrile and $[d_2]$ 2-azabicyclo $[2,2,2]$ octane (Ic) as reactants in Scheme A. The labelled amine (Ic) was synthesised by reducing the corresponding lactam (Ia) with lithium aluminium deuteride. The $[d_9]$ analogue (VIc) was made incorporating $[d_9]$ 4-bromo-2,2-diphenylbutyronitrile (IIIb) in Scheme A using in this instance unlabelled amine (Ib). A Friedel-Crafts reaction[4] involving $[d_6]$ benzene and mandelonitrile with boron trifluoride as catalyst was utilised to give $[d_5]$ diphenylacetonitrile (IIb) which was then condensed with $[d_4]$ 1,2,- dibromoethane to give $[d_9]$ intermediate (IIIb).

The isotopic purity of the $[d_4]$ -, $[d_6]$ - and $[d_9]$ analogues of the 2-methyl-oxadiazole (VI) was investigated by the examination of the molecular ion regions in their mass spectra and calculations based on the m+1 ion gave the following enrichment factors, $[d_4]$ 97.8%, $[d_6]$ 98.5%, and $[d_9]$ 96.2%.

EXPERIMENTAL

In general organic extracts were dried over sodium sulphate and solvents were removed on a rotary evaporator under vacuum. The products were characterised by their melting point, spectral and chromatographic properties. Mass spectral analysis was performed on a Finnigan 3200E gas chromatographic mass spectrometer with a chemical ionisation source using methane as the reactant gas at a source

temperature of 150°C and pressure 0.70 Torr. Data was analysed by a Finnigan 6000 on-line data system. Proton NMR spectra (60 MHz) were recorded on a Varian EM360 using tetramethylsilane as internal standard. Thin layer chromatographic analysis was performed on Kieselgel $60F_{254}$ silica gel precoated plates. Lithium aluminium deuteride and [d_4] 1,2-dibromoethane were supplied by Merck Sharpe and Dohme (Canada) and [d_6] benzene by NMR Ltd. High Wycombe. All deuterated starting materials had a minimum isotopic purity of 99 atom %D. All the labelled compounds showed identical properties to non-labelled counterparts on chromatography and exhibited the physical and spectral properties expected from comparison with the unlabelled compounds.

[d_4]4-Bromo-2,2-diphenylbutyronitrile (IIIa)

Sodamide (5 g, 116 mmole) was quickly added to a solution of diphenylacetonitrile (11.1 g, 58 mmole) in dry benzene (75 ml) kept under a nitrogen atmosphere at 10°C and the mixture was stirred for 4½ hours. To the resulting solution was added [d_4] 1,2-dibromoethane (11.59 g, 60 mmole) and stirring continued for a further 18 hours. The mixture was washed with water and on evaporation the organic solution gave an oil which solidified on trituration under hexane to give 13.36 g, (76%) of an off-white solid mp 66.5-69°C. (lit.[5] unlabelled compound mp 66-67°C). [d_9] 4-Bromo-2,2-diphenylbutyronitrile (IIIb) was prepared in a similar manner using [d_5] diphenyl acetonitrile (IIb).

[d_5]Diphenylacetonitrile (IIb)

To a mixture of mandelonitrile (50 g, .38 mole) and [d_6] benzene (23 g, .27 mole) was added boron trifluoride etherate (32.5 ml of a 48% solution, .23 mole) in one portion. The reaction mixture was kept at 80°C for 5 hours, cooled, then diluted with ether (200 ml). The organic solution was washed with a solution of sodium carbonate followed by water and evaporation gave an oil. Distillation gave 20 g (37%) of a pale yellow oil bp 140° at 2 mm (lit.[6] for unlabelled material bp 181° at 12 mm) which solidified on trituration with hexane.

[d_2] 2-Azabicyclo [2,2,2] octane (Ic)

Lithium aluminium deuteride (1 g) was suspended in dry tetrahydrofuran (10 ml) and a solution of the lactam [7,8] (Ia) (2.4 g, 19.2 mmole) in dry tetrahydrofuran (30 ml) was added over 45 minutes under a nitrogen atmosphere. The mixture was

refluxed for 18 hours and excess lithium aluminium deuteride was destroyed by the addition of 'wet' tetrahydrofuran. The filtered solution was concentrated to a small volume and diluted with ether. An ethereal solution of hydrogen chloride was added until no further precipitation occurred and the resulting solid was dried to give the amine hydrochloride (2.4 g, 84%) mp 300-306°C (lit.[8] unlabelled compound mp >300°C).

[d_4] 4-(2-Azabicyclo[2,2,2]octan-2-yl)-2,2-diphenyl butyronitrile (IVa)

The amine hydrochloride (Ib) (4 g, 27.1 mmole) was dissolved in water (20 ml), and potassium hydroxide pellets (3.34, 59.6 mmole) followed by the nitrile (IIIa) (8.92 g, 29.3 mmole), were added. The resultant mixture which became a two phase liquid mixture on refluxing was heated with stirring at reflux for 4 hours. The mixture was cooled to 60°C and benzene (75 ml) was added, and the organic extract separated. A solution of concentrated hydrochloric acid in isopropanol (2 ml) (1:4.3 / hydrochloric acid:isopropanol) was added and after reduction of the total volume to 50 ml on a hot plate, colourless crystals formed on cooling. The yield of the required amine hydrochloride was 7.14 g (71%) mp 188-190°C. The free base was obtained as a solid mp 96-97.5°C. The [d_6]- and [d_9] analogues of the free bases were prepared in a similar manner and had mp 93-97°C and mp 95-97°C respectively (lit.[1] unlabelled free base mp 96-99°C).

[d_4] 5-[1,1-Diphenyl-3-(2-azabicyclo[2,2,2]octan-2-yl) propyl]-1H-tetrazole (Va)

The amine (IVa) as the free base (5.1 g, 15.3 mmole), ammonium chloride (1.28 g, 20 mmole), lithium chloride (0.25 g, 5.8 mmole) and sodium azide (1.5 g, 23 mmole) were stirred in dimethylformamide (16 ml) at room temperature for 1 hour. A yellow solution containing undissolved white solid resulted and this mixture was slowly heated to 120°C over 2 hours then heated at this temperature for 20 hours. A white solid precipitated during this time and after cooling the product was filtered off giving 4.6 g, (83%) mp 309-310°C (lit.[1] mp for unlabelled material not reported). The [d_5]- and [d_9] analogues were obtained in the same manner and had mp 310-313°C and mp 308-310°C respectively.

[d_4] 2-[3,3-Diphenyl-3-(2-methyl-1,3,4-oxadiazol-5-yl) propyl]-2-azabicyclo[2,2,2]octane (VIa)

A suspension of the tetrazole (Va) (4.55 g, 12.5 mmole) in pyridine (28 ml) and acetic anhydride (9.25 ml, 97.9 mole) was heated to 120°C (reflux temperature)

over a period of 45 minutes and heating continued for a further 5½ hours. The resultant solution was evaporated to give an oil which was taken up in benzene (25 ml) and the solution extracted with water (4 x 15 ml) and with 5% aqueous acetic acid (4 x 15 ml). The combined aqueous extracts were adjusted to pH 10 by the addition of concentrated ammonium hydroxide solution. The gummy solid that precipitated crystallised on standing overnight. The crude product was filtered off (4.56 g) and purification was achieved by dissolution in benzene (25 ml) and passage through a neutral alumina column (10 g) activity grade 1 (Wohem) with additional benzene (25 ml). Evaporation of the total eluant gave a white solid, 3.64 g, (75%) mp 122.5-124°C (lit.[1] for unlabelled analogue mp 121-123°C). The $[d_6]$ - and $[d_9]$ analogues had mp 117-119°C and mp 121.5-123.5°C respectively. Mass spectral analysis for the d_o analogue of VI, m/e 138 (47.8), 386 (8.0),387 (3.3), 388 (100), 389 (26.5). For (VIa), m/e 142 (33.7), 390 (7.9), 391 (7.5), 392 (100), 393 (28.3). For (VIb), m/e 144 (40.4), 392 (11.1), 393 (16.4), 394 (100), 395 (27.4). For (VIc), m/e 142 (39.0), 395 (11.6), 396 (11.3), 397 (100), 398 (27.2). NMR spectral data, ($CDCl_3$) δ: for the d_o analogue of VI, 1.2-3.0 (19H,m), 7.2 (10H,s). For VIa, 1.2.-2.0 (9H,m), 2.5 (3H,s), 2.6 (1H,m), 2.7 (2H,s), 7.2 (10H,s). For VIb, 1.2-2.0 (9H,m), 2.5 (3H,s), 2.6 (1H,m), 7.2 (10H,s). For VIc, 1.2-2.0 (9H,m), 2.5 (3H,s), 2.6 (1H,m), 2.7 (2H,s), 7.2 (5H,s).

A C K N O W L E D G M E N T

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