The Synthesis of [*methylenedioxy*-^{14}C]Paroxetine BRL 29060A

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Summary

Paroxetine (1), BRL 29060A , a potent antidepressant, has been prepared radiolabelled with carbon-14 in the methylenedioxy group in 5 steps and 20.9% overall yield from [^{14}C]dibromomethane. Two altenative preparations of 3,4-[*methylenedioxy*-^{14}C]phenol (2) are also described.

Keywords: antidepressant, paroxetine, BRL 29060A, carbon-14 labelling, [*methylenedioxy*-^{14}C]phenol.

Introduction

Paroxetine (BRL 29060A), 3S,4R-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine hydrochloride (1), a selective inhibitor of 5-hydroxytryptamine (5-HT) uptake, is a potent antidepressant marketed by SmithKline Beecham. The synthesis of carbon-14 labelled paroxetine and scrambling of the label between the expected C7 exomethylene position and the C2 of the piperidine ring (see Scheme) , which occurs during the synthesis, has been described previously from these laboratories, together with carbon-13 studies which confirmed the positions of the carbon-14 label (ref. 1). Christensen *et. al.* (ref. 2) have reported a similar phenomenon in a related system. In this note we report a synthesis of alternatively labelled paroxetine , namely [*methylenedioxy*-^{14}C]paroxetine which was required for ADME studies.

Discussion

The synthesis of [*methylenedioxy*-^{14}C]paroxetine (1) is illustrated in the Scheme. Critical to the success of this synthesis was an efficient preparation of 3,4-[*methylenedioxy*-^{14}C]methylenedioxyphenol (sesamol) (2). Our strategy was to methylenate a suitably functionalised catechol and subsequently develop the phenol functionality. Two such syntheses are described below. Numerous methods are known (ref. 3) for the methylenation of catechols, usually

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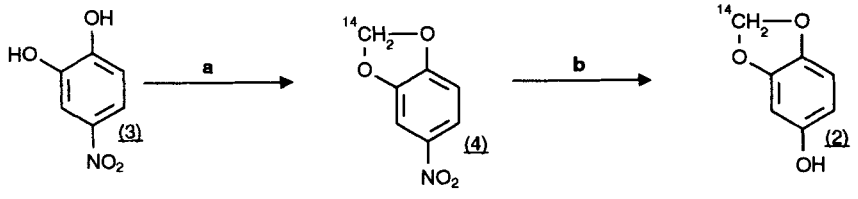
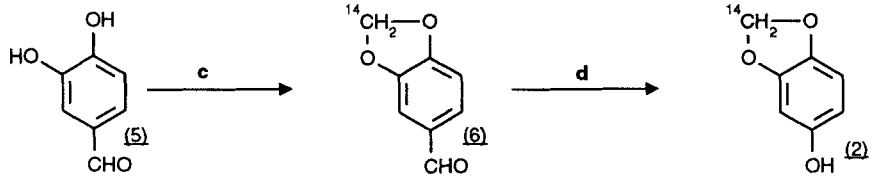
involving reaction with a dihalomethane in the presence of a suitable base. Treatment of 4-nitrocatechol (3) with [^{14}C]dibromomethane/Cs_2CO_3 (DMSO, 85°C) gave 1,2-[*methylenedioxy*-^{14}C]methylenedioxy-4-nitrobenzene (4) in 56% yield (based on dibromomethane). Alternative bases (e.g. KF, CsF) or solvents (DMF) gave no improvement in yield. Introduction of the phenol function in three steps; reduction of the nitro group (H_2, Pd/C), diazotisation (HNO_2) and decomposition of the diazonium salt ($CuNO_3$, Cu_2O, H_2O) completed the synthesis of [*methylenedioxy*-^{14}C]sesamol (2) in a modest 9.6% overall yield from [^{14}C]dibromomethane.

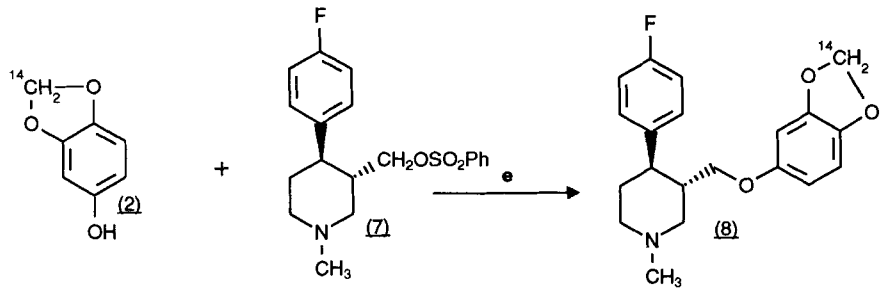
Scheme ; The Synthesis of [*methylendioxy*-^{14}C]paroxetine



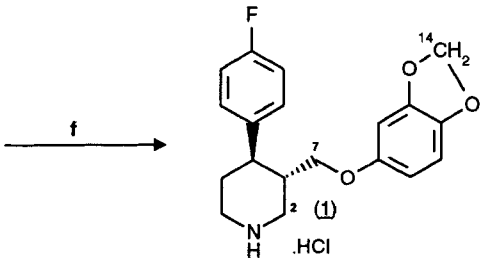
a : [^{14}C] CH_2Br_2, Cs_2CO_3, DMSO **b : i) H_2, Pd/C ii) HNO_2 iii) $CuNO_3$, Cu_2O**



c : [^{14}C]CH_2Br_2 , Cs_2CO_3, DMF **d: i) MCPBA ii) NaOH**



e : i) $NaOCH_3$ ii) DMF Δ **f : i) vinyl chloroformate, K_2CO_3, ii) HCl, EtOH, Δ**



[*methylenedioxy*-^{14}C]paroxetine BRL 29060A

This route has two major drawbacks: i) the powerful electron withdrawing nature of the nitro group allows only a moderate yield for the methylenation of 4-nitrocatechol (3) and ii) decomposition of the diazonium salt is a capricious and inefficient process. Consequently an alternative route was developed. A phenol function can be readily introduced by Bayer-Villager oxidation of an aryl aldehyde and hydrolysis of the resultant formate ester. 3,4-Dihyroxybenzaldehyde (5) was smoothly methylenated with [^{14}C]dibromomethane/Cs_2CO_3 (DMF 110-120°C) furnishing 3,4-[*methylenedioxy*-^{14}C]methylenedioxybenzaldehyde (6) in 89% yield. Bayer-Villager oxidation (MCPBA) and subsequent ester hydrolysis (NaOH) yielded 3,4-[*methylenedioxy*-^{14}C]sesamol (2) in 67.2% overall from dibromomethane. Reaction of the sodium salt of [*methylenedioxy*-^{14}C]sesamol (2) and 3S,4R-4-(4-fluorophenyl)-1-methyl-3-(phenylsulfonyloxymethyl)piperidine (7) (DMF, 50°C) smoothly furnished 1-methyl-[*methylenedioxy*-^{14}C]paroxetine (8) in 61.6% yield following recrystallisation from diisopropylether. N-Demethylation, with vinyl chloroformate, completed the synthesis of the title compound (1) in 20.9% overall yield from [^{14}C]dibromomethane.

Experimental

[^{14}C]Dibromomethane was obtained from ICI-Cambridge Research Biochemicals, Billingham and 3S,4R-4-(4-fluorophenyl)--1-methyl-3-(phenylsulfonyloxymethyl)piperidine (7) was supplied by SmithKline Beecham Chemical Development Department. HPLC purification was carried out on Spherisorb 10μ silica (22.5x250mm column) eluted at 10ml/min. with EtOAc/CH_3OH/c, NH_4OH 90:10:1 (by vol.) using Gilson 303 pumps and UV detection at 254nm by a Holochrome detector. Radiochemical purities were determined by TLC with a Berthold 2832 linear analyser, integration by Berthold Chroma software, on Merck 5714 silica in the following systems i) $CHCl_3/CH_3OH$/glacial AcOH (18:2:1 by vol.) and ii) CH_3OH/H_2O/c. NH_4OH (20:7:1 by vol.) and by HPLC using a Beckman 171 radioisotope detector, integration by Beckman System Gold software, on μ-Bondapak C18 eluted with NaH_2PO_4 (pH=3.2)/CH_3CN 65:35v/v at 1.5ml/min. Quantification of radioactivity was by use of a Beckman LS6800 scintillation counter. All labelled materials were characterised by chromatographic comparison to authentic samples or by spectroscopy (NMR/MS).

1,2-[*methylenedioxy*-^{14}C]methylenedioxy-4-nitrobenzene (4)

To a stirred solution of 4-nitrocatechol (3) (397mg, 2.56mmol) in anhydrous DMSO (3ml) was added Cs_2CO_3 (1663mg, 5.1mmol) followed by [^{14}C]dibromomethane (399mg, 740Mbq, 20mCi, 2.29mmol) and the mixture heated at 85°C for 3h. The cooled reaction mixture was poured into water and exhaustively extracted with EtOAc. The combined extracts were washed with 5M NaOH, brine, dried over $MgSO_4$, filtered and evaporated to dryness, furnishing the title compound (4) (215.7mg, 1.29mmol , 56%).

3,4-[*methylenedioxy*-^{14}C]methylenedioxyphenol (2)

An ethanolic solution of 1,2-[*methylenedioxy*-^{14}C]methylenedioxy-4-nitrobenzene (4) (215.7mg, 1.29mmol) was hydrogenated, at 1atm., over 10% Pd/C (176mg) for 1.5h. The filtered solution

was evaporated to dryness, the residue dissolved in glacial AcOH (3ml) and added, dropwise, to a solution of conc. H_2SO_4 (0.730ml) in water (4ml). The resultant solution was cooled in ice, $NaNO_2$ (245mg, 3.55mmol) in water (1.1ml) added dropwise and cooling maintained for 50min, whereupon it was added to a rapidly stirred solution of $CuNO_3.5H_2O$ (100g) in water (125ml). Cu_2O (1.1g) was added immediately and the mixture stirred for 1h. The reaction mixture was extracted with ether and the combined extracts back extracted with 5M NaOH. The basic extracts were acidified and re-extracted with ether, the combined extracts dried over a mixture of $MgSO_4$ and K_2CO_3, filtered and evaporated to dryness giving the title compound (2) (29.9mg, 0.22mmol, 9.6% overall from dibromomethane).

3,4-[*Methylenedioxy*-^{14}C]methylenedioxybenzaldehyde (6)

3,4-Dihydroxybenzaldehyde (5) (897mg, 6.5mmol) and Cs_2CO_3 (4240mg, 13.0mmol) were stirred in degassed anhydrous DMF (7ml) under nitrogen for 30min. and [^{14}C]dibromomethane (1025mg, 9250Mbq, 250mCi, 5.89mmol) added. The mixture was heated at 110-120°C for 4h, cooled, filtered, the filtrate diluted with water (100ml) and exhaustively extracted with ether. The combined extracts were dried over $MgSO_4$, filtered and evaporated to dryness giving the title compound (6) as a yellow crystalline solid (786.6mg, 89.0%).

3,4-[*Methylenedioxy*-^{14}C]methylenedioxyphenol (2)

3,4-[*Methylenedioxy*-^{14}C]methylenedioxybenzaldehyde (6) (786.6mg, 5.24mmol) was dissolved in CH_2Cl_2 (10ml) and MCPBA (1260mg, 5.80mmol, 80% pure) in CH_2Cl_2 (5ml) added dropwise. The mixture was stirred at ambient temperature for 20h, diluted with CH_2Cl_2, washed successively with 10% aqueous Na_2CO_3 and water, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was dissolved in CH_3OH (5ml), 5M NaOH (10ml) added and the reaction stirred for 1h, diluted with water (25ml) and extracted with ether. The aqueous layer was acidified (5M HCl) and thoroughly extracted with ether. On drying and evaporation the extracts yielded the title compound (6) as a purple oil (648.9mg). This crude material was purified by filtration through a bed of silica (eluted with ether) furnishing (6) as a yellow crystalline solid (546.9mg, 3.96mmol, 67.2% yield from [^{14}C]dibromomethane).

1-Methyl-[*methylenedioxy*-^{14}C]paroxetine (8)

3,4-[*Methylenedioxy*-^{14}C]methylenedioxyphenol (2) (546.9mg,3.96mmol) was dissolved in CH_3OH (2ml) and $NaOCH_3$ (2.496ml of a 1.60M solution in CH_3OH, 4.0mmol) added, the mixture stirred for 15min and evaporated to dryness. The sodium salt was dissolved in anhydrous DMF (10ml) and 3S,4R-4-(4-fluorophenyl)-1-methyl-3-(phenylsulfonyloxymethyl)piperidine (7) (1437mg, 3.96mmol) added. The reaction mixture was heated, under nitrogen, for 18h at 50°C, cooled, poured into water (25ml) and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered and evaporated to dryness affording crude N-methyl-[*methylenedioxy*-^{14}C]paroxetine (8) (1228mg, 87.5%). This crude product was recrystallised from diisopropylether giving the title compound (8) as yellow needles (864mg, 61.6%) of >97% radiochemical purity as

assessed by TLC. The mother liquors of crystallisation contained a second less pure (92.6% RCP) batch (366mg).

[*Methylenedioxy*-^{14}C]paroxetine, BRL 29060A (1)

N-methyl-[*methylenedioxy*-^{14}C]paroxetine (8) (303.4mg, 0.88mmol) was dissolved in anhydrous 1,2-dichloroethane (8ml), anhydrous K_2CO_3 (1.20g, 8.57mmol) and vinyl chloroformate (600µl, 0.7mmol) added. The mixture was heated at reflux, under nitrogen, and the course of the reaction followed by TLC. Further amounts of vinyl chloroformate (950µl, 1.10mmol in all) and K_2CO_3 (1.80g, 12.86mmol in all) were added over 12.25h until reaction was judged complete. The solids were filtered off and the filtrate evaporated to dryness. The residue was dissolved in anhydrous 1,2-dichloroethane and HCl gas bubbled through for 15min., and the solution stirred for a further 20min. The solvent was removed, the residue redissolved in EtOH , heated at reflux for 1.5h., and evaporated to dryness. The residue was taken up in EtOAc, washed with 1M NaOH, water, dried over $MgSO_4$, filtered and evaporated to dryness (301mg). The crude product was purified by HPLC giving a light yellow oil (218.9mg), which was converted to the hydrochloride salt (HCl/IPA) and recrystallised from IPA giving the title compound (1) as colourless needles (178.1mg, 0.49mmol, 55.4%) of specific activity 2579kBq/mg (69.7µCi/mg) and radiochemical purity ≥ 98.6% as assessed by TLC and HPLC.

References

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