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An Improved Multigram Synthesis of Tetradeuterated Buspirone

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SUMMARY

A simple, convenient and efficient two step method for the synthesis of buspirone-d_4 hydrochloride **4** from the commercially available materials is described. Tetramethylene glutarimide **1** was first N-alkylated with 1,4-dibromobutane-2,2,3,3-d_4 **2** to give a monoalkylated compound **3** which was transformed to buspirone-d_4 by alkylation with 1-(2-pyrimidyl)piperazine. This important antianxiety compound obtained in 63% yield having isotopic purity ~96% should prove useful in carrying out bioavailability studies.

KEY WORDS: Buspirone, Deuterium, Alkylation

INTRODUCTION

Buspirone (8-[4-[4-(2-Pyrimidyl)-1-piperazinyl] butyl]-8-azaspiro[4,5]decane-7,9-dione hydrochloride) is a novel psychotropic drug that has been found to be effective in the treatment of generalized anxiety disorders (1-4). It has been reported to undergo extensive first pass metabolism following oral administration

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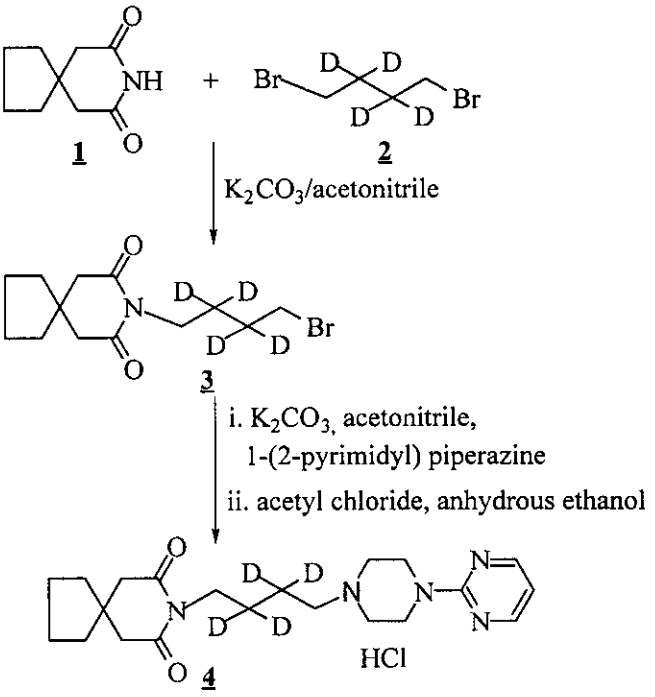
in rat, monkey (5) and man (6). The two major metabolites identified in these species are 1-(2-pyrimidyl) piperazine and 5-hydroxybuspirone. Plasma levels of buspirone are generally low even at steady state (5 ng/ml at 20 mg/Kg dose) and exhibit high variability (7).

In an effort to carry out bioavailability and bioeqivalence studies using different formulations of buspirone in animals and humans, it was decided to use stable isotope methodology. The application of stable isotopes in such pharmacokinetic and metabolic studies is well documented (8). Therefore, a stable isotope of buspirone which does not show metabolic isotopic effect and is easy to synthesize in large quantities, was needed. Earlier, synthesis of two tetradeuterated stable isotopes of buspirone labelled with deuterium at 2,2,3,3 and 3,3,5,5 carbons in the piperazine ring was reported though in low yield by a lengthy procedure involving seven and four steps respectively (9). In this report, synthesis of a different tetradeuterated analog of buspirone **4** bearing four deuterium atoms on the C-2 and C-3 carbon atoms of the butyl chain connecting the glutarimide and the piperazine moiety is presented. Since these positions are away from the site of metabolism, the metabolic isotope effect may not be observed.

RESULTS AND DISCUSSION

The synthetic route to buspirone-d_4 hydrochloride **4** is outlined in **scheme 1**. Commercially available tetramethylene glutarimide **1** in acetonitrile was reacted with 1,4-dibromobutane-2,2,3,3-d_4 **2** in the presence of anhydrous potassium carbonate to give monoalkylated product only. The unreacted 1,4-dibromobutane-d_4 was recovered by distillation and can be recycled. The monoalkylated tetramethylene glutarimide **3** was further alkylated with 1-(2-pyrimidyl) piperazine in acetonitrile in the presence of anhydrous potassium carbonate to give the desired product, buspirone-d_4 in 72% yield. Finally, it was precipitated as a hydrochloride salt from its solution in anhydrous ethanol and acetyl chloride. The overall yield of buspirone-d_4 hydrochloride was 63%.

The identity and purity of the product was confirmed by comparing its TLC with unlabelled buspirone as well as ^{1}H NMR, the mass spectroscopy (**figure 1**) and C, H, N analyses. The isotopic purity of tetradeuterated buspirone was calculated to



Scheme 1

be 95.57%. Very recently, such an analog was synthesized by passing deuterium (generated by injecting D_2O onto sodium metal under argon) through a solution of acetylenic buspirone precursor in absolute benzene using palladium catalyst in 52% yield (10). The disadvantages of such an approach are (i) the starting material- the acetylenic buspirone precursor is not commercially available. It has to be synthesized thereby making the process lengthy. Our approach uses materials which are all commercially available and cheap, (ii) the above-mentioned method utilizes nonaqueous, inert atmosphere, special apparatus and an expensive catalyst, palladium, for carrying out the reaction as well as for the generation of deuterium gas by passing deuterated water onto sodium metal. Our approach is very simple, safe and convenient to carry out and finally (iii) the yield of the reported method is low. The overall yield of tetradeuterated buspirone was increased by 11% by our method.

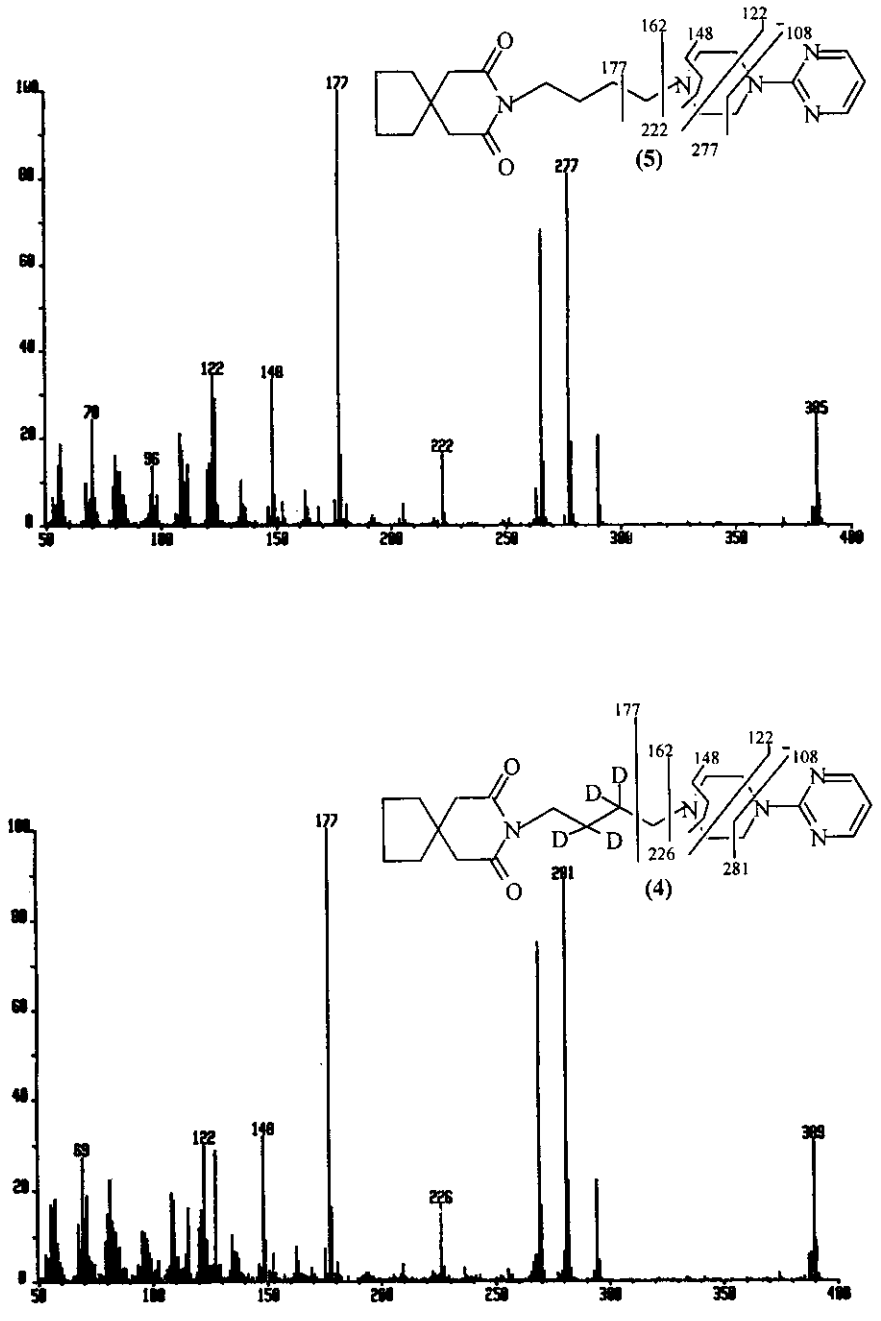


Figure 1: Electron impact mass spectra and fragmentation of buspirone (**5**) and buspirone-d_4 hydrochloride (**4**).

EXPERIMENTAL

General

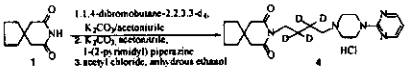
All solvents and reagents were of analytical grade and were used without purification. Tetramethylene glutarimide and 1-(2-pyrimidyl) piperazine were purchased from Acros, New Jersey, USA and Aldrich Chemical Co., Milwaukee, USA respectively. 1,4-Dibromobutane-2,2,3,3-d_4 (98.8 atom % D) was purchased from CDN isotopes, Quebec, Canada. Thin layer chromatography (TLC) was performed on 0.25 mm thick silica gel plates (Merck silica gel 60 F_{254}) using a solvent system of chloroform: methanol (7:3). Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. The proton nuclear magnetic resonance (^{1}H NMR) spectra were determined using a Bruker AM 500 FT NMR machine (500 MHz). Chemical shifts are reported in parts per million downfield from tetramethylsilane. Mass spectra were obtained using a VG Micromass 7070 HE instrument connected to a DEC PDP 11-2505 data system.

Synthesis of 8-(4-Bromobutyl-2,2,3,3-d_4)-8-azaspiro[4,5] decane-7,9-dione **3**

A mixture of 8-azaspiro [4,5] decane-7,9-dione (0.03 mol), 1,4-dibromobutane 2,2,3,3-d_4 (0.12 mol, 98.8 atom % D) and anhydrous potassium carbonate (0.06 mol) in acetonitrile (200 ml) was heated under reflux for 14 hours. The reaction mixture was allowed to cool to room temperature and filtered through a bed of celite to remove potassium carbonate. The clear solution so obtained was evaporated under reduced pressure to remove acetonitrile. The remaining liquid was then distilled under reduced pressure (1.5 mm Hg/40°C) to remove the unreacted 1,4-dibromobutane-d_4. A syrupy reddish liquid was left behind. It was chromatographed on silica gel column and the compound was eluted using hexane: ethyl acetate (2:1) as eluent. Fractions containing the alkylated product were combined and evaporated under reduced pressure to give an oily product. The yield of compound **3** was 77.92%. ^{1}H NMR ($CDCl_3$) δ: 1.45-1.52 (m, 4H, CH_2), 1.64-1.74 (m, 4H, CH_2), 2.56 (s, 4H, CH_2CO), 3.36 (s, 2H, CH_2NCO), 3.75 (s, 2H, CH_2Br).

Synthesis of 8-Azaspiro[4,5]decane-7,9-dione, 8-[4-[4-(2-pyrimidyl)-1-piperazinyl] butyl-2,2,3,3-d_4] hydrochloride **4**

A mixture of compound **3** (0.05 mol), 1-(2-pyrimidyl) piperazine (0.05 mol) and anhydrous potassium carbonate in acetonitrile (0.01 mol) was heated under reflux for 12 hr. The reaction mixture was filtered through a bed of celite and the solvent was removed in vacuo affording a solid that upon recrystallization from 2-propanol yielded 80.04% buspirone-d_4 as a white product. A solution of buspirone-d_4 base in ethanol was added to a solution of acetyl chloride in anhydrous ethanol and the mixture was kept in a refrigerator. A white crystalline material was filtered, dried and recrystallized from acetonitrile. M.P. 192-194 ^{0}C; ^{1}H NMR ($CDCl_3$) δ: 1.44-1.52 (m, 4H, CH_2), 1.62-1.72 (m, 4H, CH_2), 2.6 (s, 4H, CH_2CO), 3.1 (s, 4H, CH_2), 3.62-3.78 (m, 4H,CH_2), 4.06-4.2 (m, 2H, CH_2), 5.06-5.16 (m, 2H, CH_2), 6.92-6.98 (br, 1H, p-Ar), 7.24 (s, 2H, m-Ar), 13.04 (br, 1H, +NH); Anal. calculated for $C_{21}H_{28}D_4N_5O_2Cl$: C, 59.21, H, 7.56; N, 16.44. Found: C, 59.12; H, 7.57; N, 16.27. Estimated tetradeuterium incorporation 95.57 %.



CONCLUSION

In conclusion, buspirone-d_4 was synthesized in 2 steps, starting from tetramethylene glutarimide and 1,4-dibromobutane-2,2,3,3-d_4. The overall yield was 63% and the isotopic purity of buspirone-d_4 was 95.57%.

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