SYNTHESIS OF IMIPRAMINE LABELLED WITH FOUR DEUTERIUM ATOMS IN 10, 11 POSITIONS

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SUMMARY

The synthesis of imipramine labelled with four deuterium atoms in 10, 11 positions is described. The intermediate, trideutero-o-nitrotoluene was prepared by reduction of o-nitrobenzoic acid with B_2D_6 followed by conversion of the resulting alcohol to the chloride and selective reduction of the chloride with $NaBD_4$ in dimethyl sulfoxide. Trideutero-o-nitrotoluene was then converted to tetradeutero-2,2'-dinitrodibenzyl by treatment with K-tert butoxide in presence of air. The dinitro compound was reduced to a diamino compound which was then cyclized by heating its diphosphate salt, and the resulting amine on reaction with 1-chloro-3-dimethylaminopropane gave tetradeuterated imipramine.

Key words: Imipramine-d_4, o-Nitrotoluene-d_3, 2,2'-Dinitrodibenzyl-d_4,

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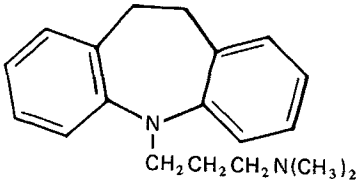
0362-4803/81/081189-08$01.00

Received July 7, 1980
Revised August 13, 1980

INTRODUCTION

One of the recent methods for comparing relative bioavailability of different formulations of a drug is based upon the comparison between the formulation to be tested and its stable isotope labelled variant that is taken orally in solution at the same time the tested formulation is ingested. The drug concentrations in the plasma are then measured by sensitive analytical methods. Recently, Heck et al (1) have studied bioavailability of two commercially available imipramine (1) tablets relative to d_2-labelled imipramine in aqueous solution using high pressure liquid chromatography and field ionization mass spectrometry for the measurement of imipramine (2). Alkalay et al (3) of our laboratory have developed a very sensitive gas chromatography mass spectrometry (GC-MS) method with selected ion monitoring for the measurement of imipramine. The ion at m/e 220 was selected for this purpose which is chemically represented by Structure 2. For bioavailability studies of imipramine by this method, we needed stable



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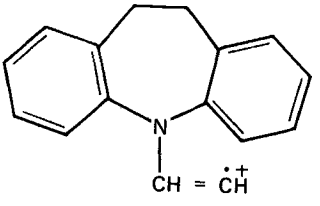

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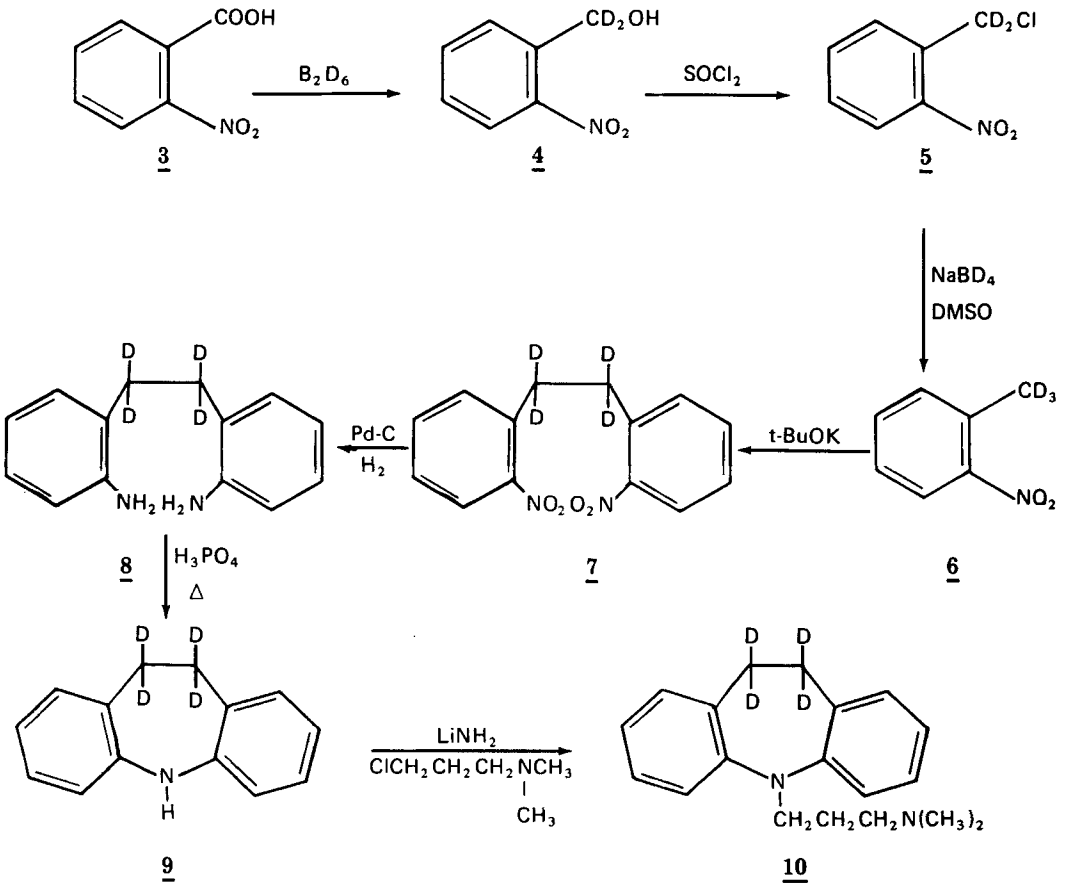
isotope labelled imipramine having the molecular weight of at least 3 mass units higher for optimum sensitivity. Previously, imipramine labelled with more than three deuterium atoms has been prepared by acid catalyzed exchange reactions (2,4). But these materials were mixtures of several deuterated species unsuitable for our studies. We have prepared tetradeuterated imipramine having all the deuterium atoms in the 10, 11 positions by chemical synthesis which is described in this paper.

METHODS AND RESULTS

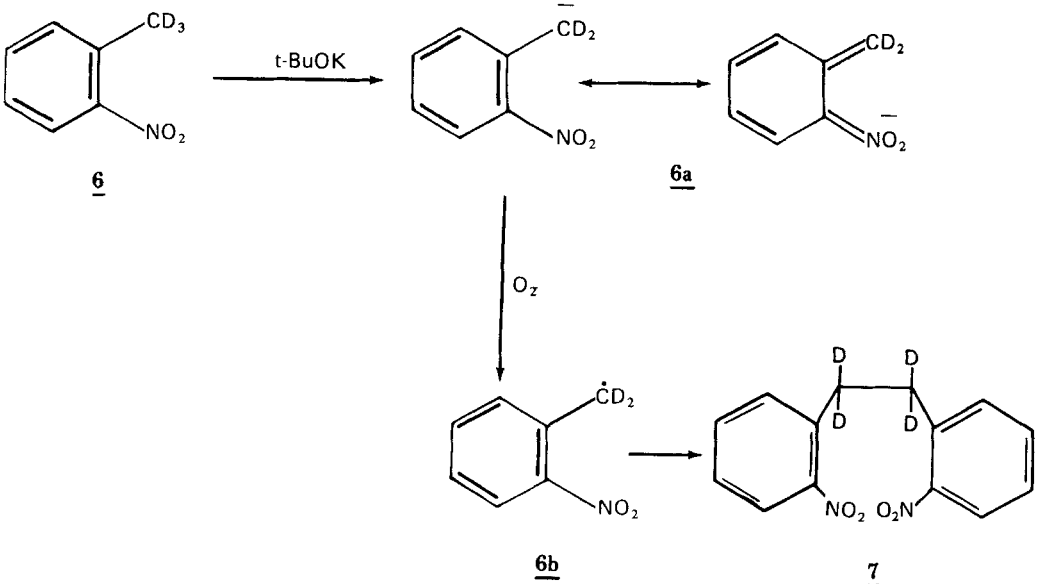
The reaction sequence for the synthesis of d_4-imipramine (10) is shown in Scheme 1.

Scheme 1



3 4 5 6 7 8 9 10

o-Nitrobenzoic acid (3) was reduced with deuterated borane to give deuterated o-nitrobenzyl alcohol (4) which was converted to the chloride 5 by reaction with thionyl chloride. When 5 was treated with sodium borodeuteride in dimethyl sulfoxide, selective reduction of the CD_2Cl group took place giving trideutero-o-nitrotoluene (6). Treatment of 6 with sodium ethoxide and isoamyl or ethyl formate under the conditions used for the preparation of 2,2'-dinitrodibenzyl from o-nitrotoluene (5) did not give any appreciable amount of 7. However, when sodium ethoxide was replaced by a stronger base, potassium tertiary butoxide, 7 was obtained in a very good yield. It was also observed that ethyl or isoamyl formate was not required if the reaction was carried out in presence of air or oxygen. Some unsymmetrical 2,2'-dinitrodibenzyl derivatives have previously been synthesized by this method (6). We believe that the reaction proceeds first with the formation of the resonating ion 6a by the action of potassium tertiary bu-



6 6a 6b 7

toxide on 6. The ion 6a is then oxidized by oxygen to the radical 6b which on dimerization gives 2,2'-dinitro-tetradeuterodibenzyl (7). Apparently sodium ethoxide is not basic enough to convert 6 into 6a.

The diamine 8 was prepared by catalytic hydrogenation of 7 and its diphosphate salt was heated at 300° to give tetradeuterated amine 9 which on reaction with 1-chloro-3-dimethylaminopropane in the presence of lithium amide gave tetradeuterated imipramine (10).

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance (Nmr) spectral data are reported in parts per million (ppm) relative to tetramethylsilane. Nmr spectra at 90 MHz were recorded on a Varian EM-390 spectrometer and the mass spectra were obtained on an AEI MS-902 instrument. Thin layer chromatography (tlc) was carried out on silica gel 60 F 254 plates of 0.5 mm thickness.

o-Nitrobenzyl alcohol-d_2 (4). To a solution of 300 ml of 1 M borane-d_3 in tetrahydrofuran was added a solution of 50.1 g (300 mmol) of o-nitrobenzoic acid in 50 ml of tetrahydrofuran with magnetic stirring. The solution was then refluxed for 4 hours. The reaction mixture was then decomposed by dropwise addition of water and tetrahydrofuran removed by evaporation in vacuo. The residue was treated with saturated NaCl solution and then extracted with ether. The ether extract was washed with $NaHCO_3$ solution and dried with $MgSO_4$. Evaporation of ether gave 44.0 gm (96% yield) of a colorless oil which solidified on standing. A small sample was crystallized from ethyl acetate-petroleum ether mixture to give a white solid, m.p. 70-72° [reported (7) m.p. of o-nitrobenzyl alcohol 74°].

o-Nitrobenzyl chloride-d_2 (5). To a solution of 43.8 g (286 mmol) of o-nitrobenzyl alcohol-d_2 in 150 ml of chloroform and 23 g of pyridine was added 35.7 g (300 mmol) of thionyl chloride. The reaction mixture was stirred

overnight at room temperature and then treated with ice and HCl (excess). The chloroform solution was dried with $MgSO_4$ and then evaporated to dryness in vacuo to give 48.0 gm (98% yield) of a light yellow oil. A small portion was crystallized from ethyl acetate-petroleum ether to yield a white solid, m.p. 49-51° [reported (7) m.p. of o-nitrobenzyl chloride 50-52°].

o-Nitrotoluene-d_3 (6). To a mixture of 15.0 g (358 mmol) of $NaBD_4$ in 150 ml of dimethylsulfoxide was dropwise added a solution of 46.0 g (265 mmol) of o-nitrobenzyl chloride-d_2 in 50 ml of dimethylsulfoxide at room temperature. After an induction period, the reaction became exothermic and needed cooling with ice-water. After the vigor stopped, the mixture was stirred for 2 hours at room temperature and then 200 ml of water was slowly added to it. The product was isolated by extraction with ether. The ether solution was dried with $MgSO_4$ and then evaporated to dryness. The residual oil was distilled (b.p. 112-14° at 12 mm) to give 36.0 gm of an oily product (97% yield).

Analysis: Calcd for $C_7H_4D_3NO_2$: C, 59.99; N, 9.99. Found C, 60.24; N, 10.03.

2,2'-Dinitrodibenzyl-d_4 (7). To an ice-cooled solution of 21.0 g (150 mmol) of o-nitrotoluene-d_3 in 50 ml of ether was added in 4 portions a total of 19.0 g (165 mmol) of potassium tert-butoxide. The mixture was stirred at room temperature overnight and a slow stream of dry air was passed through the reaction flask. The mixture was then poured onto ice-water and extracted with ether. The ether solution was dried with $MgSO_4$ and evaporated to dryness to give 13.7g of a solid (65% yield) which was crystallized from ethyl acetate-petroleum ether, m.p. 114-17° [reported (5) m.p. of 2,2'-dinitrodibenzyl 123°].

10,11-Dihydro-5H-dibenz[b,f]azepine-d_4 (9). A solution of 12.0 g (46 mmol) of 2,2'-dinitrodibenzyl-d_4 in 100 ml of dioxane containing 2.0 g of 10% palladium on charcoal was hydrogenated at 45 psi for 1 hour. The mixture was filtered and two equivalents of 85% phosphoric acid was added to it. The resulting white solid was filtered to give 18.0 g of the phosphate salt, m.p. 256-59° [reported (5) m.p. of the non-deuterated compound 266-68°]. The above salt was then heated in a nitrogen atmosphere at 295° for 20 minutes. The melt was cooled and treated with 2N NaOH solution and then extracted with ether. The ether extract was dried and evaporated to dryness. The residue was chromatographed on a column of silica gel using toluene as the eluting solvent. Evaporation of the solvent from the eluate gave 5.0 g (55% yield) of 9 m.p. 105-108° [reported (5) m.p. of the non-deuterated compound 104-105°).

Imipramine-d_4 (10). A mixture of 10.5 g (57.7 mmol) of 9, 8.3 g (68.5 mmol) of dimethylaminopropyl chloride and 1.6 g of lithium amide in 30 ml of toluene was refluxed overnight. The reaction mixture was poured onto ice water and extracted with ether. The ether extract was then mixed with excess of 3 N HCl solution by shaking. The aqueous layer was separated from the ether layer and basified by the addition of NaOH solution and extracted with ether. The ether extract was dried with $MgSO_4$ and evaporated to dryness to give an oil which was converted to its oxalate salt. The oxalate salt was purified by crystallization from ethanol-ether. Pure imipramine-d_4 was then generated from the oxalate salt by the addition of NaOH solution and extraction with ether. The ether solution was dried with $MgSO_4$ and then treated with HCl gas dissolved in ether. The hydrochloride salt was twice crystallized from isopropanol-ether (1:2) to give 10.4 g (57% yield) of a white solid, m.p. 169-171° [reported (8) m.p. of imipramine hydrochloride m.p. 174-75°].

Analysis. Calcd. for $C_{19}H_{21}D_4ClN_2$: C, 71.11; N, 8.73.

Found: C, 71.30; N, 8.51

Mass spectrum: shows peaks at m/e 284 (molecular ion of the free base), 239 [M-NH$(CH_3)_2$].

Deuterium Content: 96.1% by Nmr spectroscopy

95.9% by Mass spectrometry; d_4 compound: 85.3%, d_3 compound: 13.4%, d_2 compound: 1.3% by multiple peak monitoring mass spectrometry.

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