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DEUTERIATION OF RS 87476

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SUMMARY

Deuteriation of toluidine in ^2H_2O and synthesis of N-[(d_5-phenyl phenyl)methyl] piperazine are described .These intermediates permit the incorporation of 7 deuterium atoms into RS 87476 . This efficient synthesis of polydeuterated RS 87476 facilitated its use in preliminary animal studies and as an internal standard in RS 87476 quantification.

key words : N-[[5-methyl-2-[(2,6-$^2H_2$)-4-methyl-phenyl]methyl]-N'-[(d_5-phenyl-phenyl)-methyl]-piperazine , trihydrochloride; RS 87476 , determination of ; pharmacokinetics of ; internal standard .

INTRODUCTION

RS 87476 (1-[(2-(4-methyl-phenyl)-5-methyl)-1H-imidazol-4-yl-methyl]-4-diphenyl-methyl-piperazine, a novel lipophilic compound with class III calcium antagonist properties [1,2] believed to exhibit beneficial effects in cerebral ischemia, possesses different putative metabolic sites . A deuteriated form of this compound labelled on both halves of the molecule would be an aid in preliminary animal studies to assess disposition . The isotopic pattern of the deuteriated / undeuteriated blend should be preserved in animal samples to permit successful detection by mass spectrometry . We describe in this paper a convenient and efficient synthesis of RS 87476 with five deuterium atoms incorporated in phenyl-methyl piperazine and two in the tolyl moieties .

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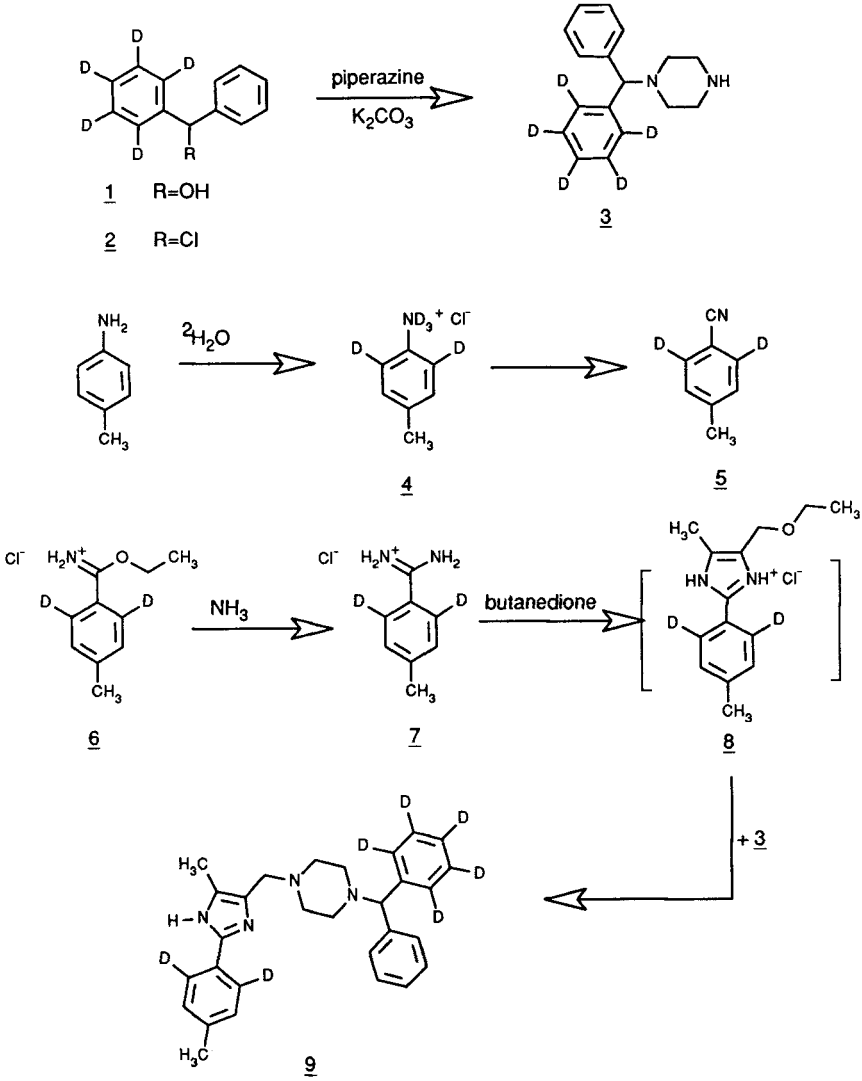
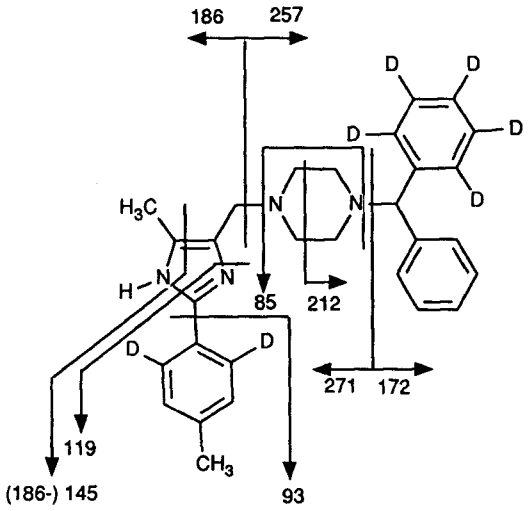
RESULTS AND DISCUSSION

A modified procedure of W.Ripka and D.Applequist [3] was used for the 2,6 dideuteriation of 4-toluidine . A mixture of 4-toluidine and ^2H_2O in the molar ratio of 1/9 was refluxed under nitrogen for 24 hours . After evaporation of the solvent the residue was dried . The percentage of deuterium incorporated , determined by NMR , was nearly quantitative under these conditions (99.6%). 4 was then converted to the nitrile 5 by a Sandmeyer reaction [4]. The imidoate 6 was obtained by addition of hydrogen chloride to the nitrile in ethanol, and treatment of this with ammonia gave the corresponding amidine 7 .



Scheme I

The labelled diphenyl-methyl-piperazine was obtained by addition of the Grignard reagent derived from bromo-d_5-benzene to benzaldehyde leading to the carbinol 1 which was chlorinated using hydrogen chloride and substituted giving the piperazine 3 . Finally 2,3-butadione was added to the amidine 7 giving the intermediate ethyl ether 8 which reacts in situ with the piperazine 3 to afford 9 in good yield as described previously [5] (scheme 1) . The mass spectra of 9 , under chemical ionization (as well as the ^{1}H NMR , aromatic region), clearly show the incorporation of 7 deuterium atoms (scheme 2).



Scheme II

EXPERIMENTAL PART

Materials and methods.

Melting points were determined on a Kofler apparatus and are uncorrected .^{1}H-NMR spectra were recorded at 200 MHz on a Brucker instrument ; chemical shifts are given in ppm relative to tetramethylsilane.

Mass spectra were recorded on a Finnagan MAT-311 A instrument using chemical ionization at 70 eV and 180°C. Micro analysis were performed by Atlantic Microlab Inc . IR spectra were measured on a Perkin Elmer M 257 spectrometer. Flash chromatography was performed on 230-400 mesh silica gel.

^2H_2O (100 atom % D) and bromo-d_5-benzene were obtained from Janssen .

[2,6-$^2H_2$-]-4-Toluidine 4 . 20 g (0.139 mol) of 4-toluidine hydrochloride in $^2H_20$ (25 ml) were refluxed under nitrogen overnight . The solvent was evaporated and the residue dried in vacuo at 55°C. ^{1}H-NMR (DMSO); 7.3 (s, 2H, aromatic) ; 2.3 (s, 3H, CH_3) .

d_5-Phenyl-phenyl carbinol 1 . To a suspension of magnesium 4.8 g (0.2 mol) and one iodide crystal in 15 ml of diethylether , was added dropwise, so as to maintain a gentle reflux a solution of bromo-d_5-benzene 25 g (0.154 mol) in 60 ml of diethylether . After the addition reflux was maintained for a further 0.5 hour . The reaction mixture was then cooled to room temperature . A solution of benzaldehyde 17 g (0.162 mol) in 60 ml of diethylether was added and the mixture was heated to reflux for 0.5 hour then cooled to 0°C and hydrolysed with 1 N HCl (80 ml) . The organic layer was dried (Na_2SO_4). The crude product obtained by evaporation of the solvent was triturated with n-heptane to give 17.5 g (yield 60%) of white crystals . ^{1}H-NMR ($CDCl_3$); 7.25 (m , 5H , aromatic) ; 5.75 (s , 1H ,CHOH); 2.55 (br s, 1 H, OH)

Chloro d_5-phenyl phenyl methane 2. A solution of 1 17g (0.090 mol) in 300 ml of diethylether at 0°C was saturated with dry gazeous HCl. After 48 hours of reaction at room temperature the solvent was removed in vacuo to give 18.7 g of a pale yellow oil (Yield = 100%) and was used in the next step without further purification . ^{1}H NMR ($CDCl_3$) 7.45-7.20 (m, 5H, aromatic); 6.10(s, 1 H, CHCl).

N-[(d_5-phenyl phenyl) methyl] piperazine 3 . A solution of 2 18.7 g (0.090 mol) in 50 ml of butanone was added dropwise to a suspension of anhydrous piperazine 30.96 g (0.36 mol) , K_2CO_3 12.42 g (0.090 mol) and KI 14.94 g (0.090 mol.). The mixture was heated under reflux for 18 hours , then filtered and the solvent was removed in vacuo .The residue was dissolved in CH_2Cl_2 (50 ml) and washed with water (15 ml). Drying and removal of the solvent followed by flash-chromatography (CH_2Cl_2: CH_3OH: NH_4OH 90 / 10 /0.5) afforded 3 as a white solid (12.5 g, 53%). ^{1}H NMR ($CDCl_3$) ; 7.5 (m, 5H, aromatic); 4.23 (s, 1H, CH); 2.8 (br, m, 4H); 2.2 (br, m, 4H); 1.6 (s, 1H, NH).

[2,6-$^2H_2$]-4-Tolunitrile. 5 . A solution of sodium cyanide 21.65 g (0.44 mol) in 40 ml of water was added to a suspension of cuprous chloride 16.5 g (0.17 mol) in 60 ml of water and the mixture was

stirred whereupon the cuprous chloride passed into solution with evolution of heat . The mixture was then cooled to 0°C (solution A).

To a solution of 4-toluidine 4 19.3 g (0.13 mol) in 80 ml of 6 N hydrochloric acid solution at 0°C was added a solution of sodium nitrite 11.26 g (0.163 mol) in 20 ml of water with stirring. The temperature of the resulting solution was kept at 0-5°C . The mixture was then neutralized with sodium hydroxide 4N at 0°C . 50 ml of toluene were poured onto surface of the cold cuprous cyanide solution (solution A) and to this mixture was slowly added the cold neutralized diazonium solution with vigourous stirring while keeping the temperature at 0-5°C. After addition, the temperature was maintained below 5°C for 0.5 hour then warmed at 50°C for 2 hours . After cooling , the mixture was washed with diethylether (5x40 ml). The combined ether fractions were filtered through a bed of silica gel and dried (Na_2SO_4) . The solvent was evaporated and the residue purified by flash chromatography (diethylether : n-heptane 10 / 90) afforded 5 as a colorless solid (5.5 g , yield = 35 %) . ^{1}H-NMR ($CDCl_3$); 7.28 (s, 2H, aromatic); 2.4 (s, 3H, $C\underline{H}_3$). I.R 2200 cm^{-1} (CN).

Ethyl [(2,6-$^2H_2$)-4-methyl-phenyl-imidoate , hydrochloride 6 . A solution of 5 10g (0.084 mol) in diethylether 200 ml and ethanol 20 ml was saturated with gazeous HCl at 0°C. The reaction mixture was allowed to stand overnight at room temperature. The excess of hydrochloric acid was then removed by a nitrogen current. The suspension of crystals was cooled down , filtered and dried in vacuo at 25°C, affording 15.77 g of 6 (yield = 93%) and were used in the next step without further purification : ^{1}H-NMR ($CDCl_3$); 11.5 (br, 2H, $N\underline{H}_2$) ; 7.45 (s, 2H, aromatic) ; 4.7(q, J=7.2, 2H, O-$C\underline{H}_2$-CH_3) ; 2.4 (s, 3H, $C\underline{H}_3$-ar); 1.5 (t, J=7.2, 3H, CH_2-$C\underline{H}_3$).

[(2,6-$^2H_2$)-4-Methyl-phenyl-amidine ,hydrochloride 7. A solution of 6 12.33g (0.061 mol) in 100 ml of methanol was saturated with gazeous ammonia . Methanol was then removed in part (2/3 vol.) To the mixture was added isopropyl acetate (100 ml) affording white crystals which were filtered and dried in vacuo at 30°C , providing 10.34 g (yield = 98%). ^{1}H-NMR ($CDCl_3$) ; 8.7 (br, 4H, $N\underline{H}_2$,$N\underline{H}$,$\underline{H}$Cl) ; 7.45 (s, 2H, aromatic) ; 2.45 (s, 3H, $C\underline{H}_3$-ar).

N-[[5-methyl-2-[(2,6-$^2H_2$)-4-methyl-phenyl]methyl]-N'-[(d_5-phenyl-phenyl)-methyl]-piperazine , trihydrochloride. 9 . To a stirred solution of 7 8.63 g (0.050 mol) in ethanol 135ml was added butanedione 4.73g (0.055 mol). The reaction mixture was refluxed for 18 hours then cooled to room temperature . To this solution were added 3 12.3 g (0.048 mol), water 70 ml and 8.23 ml of 8.75 N

NaOH solution (0.072 mol) then lithium bromide 4.59 g (0.053 mol). The mixture was refluxed for 4 hours affording a white solid which was filtered , washed with a mixture of ethanol/water (60/40) 70ml and dried to give 19.6 g (yield = 92% from 8). ^{1}H-NMR ($CDCl_3$); 7.6 (m, 8H, aromatic + NH) ; 4.17 (br s, 1H, CH) ; 3.5 (br s, 2H, CH_2-N) ; 2.75-2 (m, 14H, $2CH_3$ + 4 CH_2). ^{13}C-NMR ($CDCl_3$); 144, 142.5, 142.3, 136.7, 128.5, 127.9, 127.7, 127.6, 127.3, 126.3, 75.5, 52.4, 51.2, 20.7, 10.7 . MS (e.i.) m/e 257, 212, 186, 172, 145, 119, 93, 85, 56 . Addition of hydrochloric acid to the free base dissolved in ethanol gave the trihydrochloride salt. mp = 215°C . Calc. for $C_{29}H_{28}{}^{2}H_7Cl_3N_4$ (553.03) : C 62.93, N 10.13 , Cl 19.26 % ; found: C 62.73, N 9.82, Cl 18.93%.

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