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Synthesis of Tetradeuterated Buspirone

D. D. Dischino[1], R. R. Covington[1], C. M. Combs[2*],
and R. E. Gammans[1]

Departments of Metabolism and Pharmacokinetics[1]
and Analytical Research[2]
Division of Pharmaceutical Research and Development
Bristol-Myers Company
Evansville, IN 47721

* Author to whom correspondence should be addressed

SUMMARY

Two methods have been developed for the synthesis of tetradeuterated buspirone. Synthesis of the title compound was accomplished by the reaction of 1-(2-pyrimidinyl)piperazine-3,3,5,5-d_4 or 1-(2-pyrimidinyl)-piperazine-2,2,3,3,-d_4 with 8-(bromobutyl)-8-azaspiro[4.5]decane-7,9-dione in refluxing acetonitrile.

Key Words: Deuterium, Buspirone, Piperazine

INTRODUCTION

Buspirone (Buspar) is a novel agent that has been found to be effective for the treatment of generalized anxiety disorder at a mean dose of 20 mg/day in divided doses (1-4). Although the mechanism by which buspirone exerts its effects on anxiety has not been eludicated, it is clear that buspirone is pharmacologically and neurochemically (5,6) distinct from benzodiazepine anxiolytics in addition to representing a new chemical

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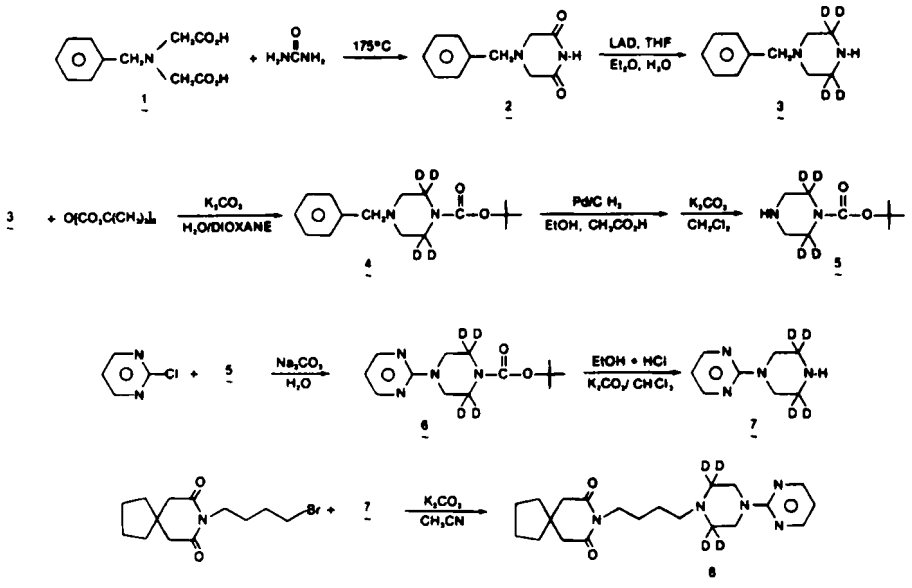
class of psychopharmacologic agents (7,8). Buspirone exhibits the properties of both a dopamine agonist and a dopamine antagonist (7,8), a characteristic to which buspirone's anxioselective action has been attributed (9). In addition, buspirone has minimal potential for abuse (10,11), does not impair psychomotor function (11,12) nor potentiate the effects of alcohol on psychomotor function (13), and is non-sedating (14). Buspirone is metabolized extensively following oral administration in rats, monkeys (15) and man (16) with 1-(2-pyrimidinyl)piperazine (1PP) and 5-hydroxy-buspirone being two principal metabolites.

Stable isotopically labeled drugs have been used extensively for a variety of metabolism and pharmacokinetic studies (17,18). The objective of our experiments was to prepare buspirone labeled with deuterium in the pyrimidinyl piperazine (1PP) moiety such that the label would be retained in the metabolite 1PP. In order to avoid an alteration of the pharmacokinetics of buspirone by a deuterium isotope effect as has been observed with captopril and nadolol (19), we felt that the deuterium should be placed on the piperazine rather than on the pyrimidinyl moiety. As a result of these studies, this report describes the preparation of 1-(2-pyrimidinyl)piperazine-3,3,5,5,-d_4 and 1-(2-pyrimidinyl)piperazine-2,2,3,3,-d_4, and the correspondingly labeled buspirone derivatives. The methods employed should be applicable to the preparation of a variety of other N,N'-disubstituted piperazine derivatives.

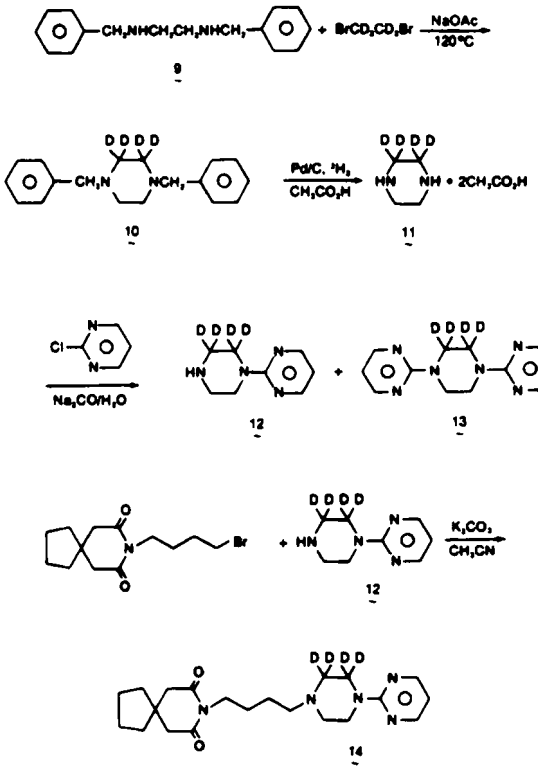
DISCUSSION

In Scheme 1 is shown the synthesis of tetradeuterated buspirone labeled in the 3 and 5 positions of the piperazine ring. In this synthesis, N-Benzyliminodiacetic acid (1) and urea are combined and reacted at 175°C to yield 4-(phenylmethyl)-2,5-piperazinedione (2) which upon reduction with $LiAlD_4$ yields 1-(phenylmethyl)piperazine-3,3,5,5-d_4 (3). Conversion of (3) to the corresponding t-BOC compound, followed by hydrogenation of (4) over Pd/C yields, (1,1-dimethylethyl)-1-piperazine-2,2,6,6-d_4 carboxylate (5). Reaction of (5) with 2-chloropyrimidine followed by removal of the protecting group yields 1-(2-pyrimidinyl)-piperazine-3,3,5,5-d_4 (7), which upon reaction with 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione yielded tetradeuterated buspirone (8).

In Scheme 2 is shown the synthesis of tetradeuterated buspirone labeled in the 2 and 3 positions of the piperazine ring. In this synthesis, N,N'-(diphenylmethyl)ethylenediamine (9) was reacted with 1,2-dibromoethane-d_4 and NaOAc at 120°C to yield N,N'-(diphenylmethyl)piperazine-2,2,3,3-d_4 (10). Hydrogenation of (10) over Pd/C in acetic acid yielded piperazine-



Scheme 1



Scheme 2

2,2,3,3-d_4 diacetate (11). Reaction of (11) with 2-chloropyrimidine yielded 1-(2-pyrimidinyl)piperazine-2,2,3,3-d_4 (12) which upon reaction with 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione yielded tetradeuterated buspirone (14).

The key fragment ions from the mass spectra of buspirone and the tetradeuterated buspirones are shown in Table 1. The mass spectrum of undeuterated buspirone shows a small mass peak at m/e 385 and a base peak of m/e 177 representing α-cleavage from the 1-(2-pyrimidinyl)piperazine radical. In addition fragments at m/e of 265 and 277 are the result of different fragmentation routes through the piperazine ring.

TABLE 1

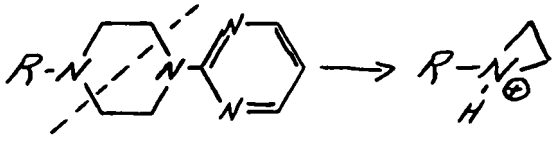
MASS SPECTRAL FRAGMENTATION OF BUSPIRONE AND ITS TETRADEUTERATED ANALOGS

COMPOUND	A	B
Buspirone	177	265
8 [a]	181	267
14 [b]	181	266, 269

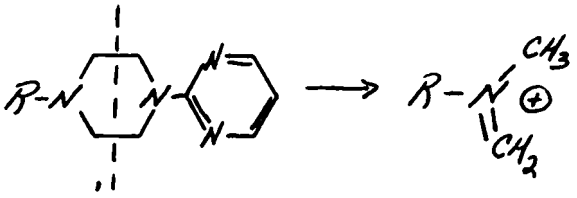
[a] 2,2,6,6 d_4 analogue

[b] 2,2,3,3 d_4 analogue

The mass spectra of the two tetradeuterated buspirones each show a mass peak of m/e 389, a base peak of m/e 181. Prior to this study it had not been possible to determine the exact fragmentation route through the piperazine ring responsible for the fragment m/e 265. An α,α fragmentation through the piperazine ring resulting in a protonated aziridinium ion is consistent for fragment m/e 267 from 8 and fragments m/e 266 and 269 from 14.



A β,β fragmentation through the piperazine ring would have resulted in fragment m/e 269 from 8 and fragment m/e 267 from 14.



Tetradeuterated t-BOC piperazine can be prepared inexpensively and in high yield via the $LiAlD_4$ reduction of 4-(phenylmethyl)-2,5-piperazinedione, followed by reaction with di-t-butyl dicarbonate and subsequent hydrogenation over Pd/C. This deuterated precursor should prove useful in preparing a variety of isotopically labeled piperazines for subsequent metabolism and pharmacokinetic studies.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded with a Perkin-Elmer R32 spectrometer for ^1H NMR and with a Varian FT-80A spectrometer for ^{13}C NMR. Chemical shifts are reported in parts per million down field from tetramethylsilane. Electron impact (70 eV) mass spectra were determined on a Finnigan 4021 GC/EI-CI mass spectrometer system.

Lithium aluminum deuteride was purchased from Aldrich Chemical Co. and 1,2-dibromoethane-d_4 was purchased from KOR Isotopes. All reagents were used without further purification.

4-(Phenylmethyl)-2,5-piperazinedione (2)

Following the procedure of Hromatka and Schramek (20), 22.3 g (0.10 mol) of N-Benzyliminodiacetic acid and 6.6 g (0.11 mol) of urea were combined, pulverized and then added to a 250 ml round bottom flask. The flask was placed in an oil bath and the temperature increased to 175°C and remained there for 1 h or until frothing discontinued. The mixture solidified on cooling and was recrystallized from aqueous ethanol to yield 12.6 g (61%) of (2) m.p. 101-103°C, lit. m.p. 105-106°C (20). ^1H NMR ($CDCl_3$) δ 3.3 (s, 4H), 3.6 (s, 2H), 7.4 (s, 5H), 9.5 (s, 1H). MS (MH^+) m/e 205.

1-(Phenylmethyl)piperazine-3,3,5,5-d_4 (3)

Into a 1 L three neck round bottom flask containing 8.2 g (0.20 mol) of $LiAlD_4$ suspended in 125 ml of dry THF was added dropwise 10.0 g (0.050 mol) of 2 in 125 ml of dry THF. After the addition was complete, the mixture

was refluxed for 2 h and then cooled in an ice bath, 125 ml of ether was added and then 10 ml of H_2O were cautiously added to the mixture. The inorganic material was filtered and extracted with THF in a Soxhlet apparatus overnight. The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to yield 5.8 g (66%) of 3 as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 1.5 (s, 1H), 2.4 (s, 4H), 3.5 (s, 2H), 7.3 (s, 5H). MS (M^+) m/e 181.

(1,1-Dimethylethyl) 4-(Phenylmethyl)-1-piperazine-2,2,6,6-d_4 carboxylate (4)
Into a 250 ml round bottom flask containing 20 ml of H_2O, 20 ml of dioxane and 2.7 g (0.019 mol) of K_2CO_3 was added 5.8 g (0.032 mol) of 3 and 7.6 g (0.035 mol) of di-t-butyl dicarbonate. The mixture was stirred at 0°C for 1 h and then at room temperature overnight. The organic solvent was removed in vacuo and the oily residue extracted with $CHCl_3$, dried ($MgSO_4$), filtered and evaporated to yield 8.3 g (92%) of crude 4 m.p. 65-68°C, recrystallization from n-hexane gave 7.5 g (83%) of 4 m.p. 69-70°C, lit. m.p. (undeuterated) 72-75°C (21). ^1H NMR ($CDCl_3$) δ 1.8 (s, 9H), 2.8 (s, 4H), 3.9 (s, 2H), 7.7 (s, 5H). MS (MH^+) m/e 281.

(1,1-Dimethylethyl) 1-piperazine-2,2,6,6-d_4 carboxylate (5)
8.7 g (0.031 mol) of (4) was dissolved in 100 ml of absolute methanol and hydrogenated over 1.3 g of 10% Pd/C in 25 ml of glacial acetic acid. After hydrogen uptake ceased, the mixture was filtered on a Celite bed, the catalyst collected, and the solvent evaporated to near dryness. The solid was then taken up in 50 ml H_2O, made basic with K_2CO_3, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo to yield 4.3 g (72%) of an oil which solidified on standing to a low melting solid, m.p. 42-44°C, lit. m.p. (undeuterated) 41°C (22). ^1H NMR ($CDCl_3$) δ 1.5 (s, 9H), 2.45 (s, 1H), 2.8 (s, 4H). MS (MH^+) m/e 191.

1-(2-Pyrimidinyl)piperazine-3,3,5,5-d_4 (7)
Into a 500 ml round bottom flask containing 37.5 g (0.270 mol) of K_2CO_3 and 175 ml of CH_3CN was added 13.0 g (0.0680 mol) of (5), 9.4 g (0.082 mol) of 2-chloropyrimidine. The mixture was then refluxed overnight with stirring, the solvent was removed and the residue dissolved in 300 ml of warm absolute ethanol. Then 70 ml of 6.5 N EtOH·HCl was added and the mixture allowed to stir at 90°C for 1 h. The mixture was cooled and filtered to yield 10.3 g (84%) of 1-(2-pyrimidinyl)piperazine-3,3,5,5-d_4 hydrochloride, m.p. 277-278°C. ^{13}C NMR (D_2O) δ 41.9, 111.5, 154.0, 157.5. MS (MH^+) m/e 169. Anal. Calc'd for $C_8H_8D_4N_4 \cdot 1.95\ HCl \cdot 0.1\ H_2O$: C, 39.85; M, 7.59; N, 23.23; Cl, 28.67. Found: C, 40.00; H, 7.65; N, 23.70; Cl, 28.45. The hydrochloride was then dissolved in 50 ml H_2O,

the solution made basic with K_2CO_3 and extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated in vacuo to yield 7.4 g (64%) of (7) as an oil.

8-[4-[4-(2-Pyrimidinyl)-1-piperazinyl-2,2,6,6-d_4]butyl]-8-azaspiro[4.5]-decane-7,9-dione (8)

4.5 g (0.027 mol) of (7), 10.5 g (0.0349 mol) of 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione and 7.4 g (0.054 mol) of K_2CO_3 in 200 ml of CH_3CN were refluxed for 8 h and then allowed to cool to room temperature. The mixture was filtered, the solvent removed in vacuo and the residue recrystallized from hot isopropanol to yield 5.0 g (48%) of (8). m.p. 100-102°C. ^{13}C NMR ($CDCl_3$) δ 24.1, 24.2, 26.0, 37.4, 39.2, 39.3, 43.4, 44.8, 52.0, 58.1, 109.6, 157.5, 161.6, 171.8. MS (MH^+) m/e 390. Anal. Calc'd for $C_{21}H_{27}D_4N_5O_2$: C, 64.75; H, 9.06; N, 17.98. Found: C, 64.82; H, 8.98; N, 18.04.

N,N'-Di(phenylmethyl)piperazine-2,2,3,3-d_4 (10)

Into a 250 ml round bottom flask containing 31.9 g (0.133 mol) of N,N'-di(phenylmethyl)ethylenediamine (9) was added 25.0 g (0.130 mol) of 1,2-dibromoethane-d_4 and 21.8 g (0.266 mol) of sodium acetate. The mixture was allowed to stir at 120°C for 4 h. The brown mixture was cooled, made basic with 1 N NaOH and extracted with benzene. The organic layer was dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue crystallized overnight and the crystals were collected and rinsed with 10 ml of methanol to yield 11.8 g (32.8%) of (10). m.p. 88-90°C, lit. m.p. 90-91°C (21). ^1H NMR ($CDCl_3$) δ 2.5 (s, 4H), 3.6 (s, 4H), 7.4 (s, 10H). Anal. Calc'd for $C_{18}H_{18}D_4N_2$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.98; H, 9.85; N, 10.51. MS (MH^+) m/e 271.

Piperazine-2,2,3,3-d_4 diacetate (11)

11.5 g (0.0425 mol) of (10) was hydrogenated over 1.0 g of 10% Pd/C in 150 ml of glacial acetic acid at room temperature. After hydrogen uptake ceased the mixture was filtered through a Celite bed, the spent catalyst separated and the filtrate concentrated in vacuo to yield 7.5 g (83.9%) of (11). m.p. 200-202°C, lit. m.p. 202-205°C (23). Anal. Calc'd for $C_8H_{14}D_4N_2O_4$. C, 45.70; H, 10.55; N, 13.32. Found: C, 45.39; H, 10.69; N, 13.35. MS (MH^+) m/e 91.

1-(2-Pyrimidinyl)piperazine-2,2,3,3-d_4 (12)

Into a 500 ml round bottom flask was added 36.5 g (0.174 mol) of (11) in 250 ml of H_2O and 25.8 g (0.243 mol) of Na_2CO_3. After the effervesence had subsided, the solution was warmed to 50°C at which time 7.95 g (0.0694 mol) of 2-chloropyrimidine was added portionwise over the next 30 min. The mixture was stirred at 50°C for 2 h and then at room temper-

ature for an additional 2 h. The mixture was cooled and the bis compound (13) was removed by filtration. The filtrate was extracted with $CHCl_3$, dried ($MgSO_4$), filtered and concentrated in vacuo to yield 7.5 g (64%) of crude (11) as a yellow oil. The crude product was then purified via flash chromatography (silica gel-CH_3CN) to yield 5.2 g (44%) of (12) which was then converted to the hydrochloride via ethanol·HCl. m.p. 277-280°C. ^{13}C NMR (D_2O) δ 41.5, 43.3, 112.1, 158.5, 158.9. MS (MH^+) m/e 169. Anal. Calc'd for $C_8H_8D_4N_4$. 1.28 HCl·0.2H_2O. C, 43.97; H, 8.16; N, 25.64, Cl, 20.77. Found: C, 44.36; H, 8.40; N, 25.63; Cl, 20.81.

8-[4-[4-(2-Pyrimidinyl)-1-piperazinyl-2,2,3,3-d_4]butyl]-8-azaspiro[4.5]-decane-7,9-dione (14)

Into a 100 ml round bottom flask containing 1.0 g (0.0045 mol) of 1-(2-pyrimidinyl)piperazine-2,2,3,3-d_4 hydrochloride hydrate in 50 ml of CH_3CN was added 1.8 g (0.0059 mol) of 8-(4-bromobutyl)-8-azaspiro[4.5]-decane-7,9-dione and 1.9 g (0.014 mol) of K_2CO_3. The mixture was refluxed with stirring for 5 h and then stirred at room temperature overnight. The mixture was filtered, the filtrate concentrated in vacuo and the residue recrystallized from hot isopropanol to yield 0.90 g (51%) of (14) as a white solid. m.p. 99.5-101.5°C. ^{13}C NMR ($CDCl_3$) δ 24.2, 26.1, 37.6, 39.3, 39.5, 43.6, 44.9, 53.0, 58.3, 109.7, 157.6, 161.7, 172.0. MS (MH^+) m/e 390. Anal. Calc'd for $C_{21}H_{27}D_4N_5O_2$. C, 64.75; H, 9.06; N, 17.98. Found: C, 64.43; H, 9.17; N, 17.65.

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