PREPARATION OF SPECIFICALLY-LABELLED BUSPIRONE -^{14}C AND BUSPIRONE - $^{15}N_2$

R. R. Covington*, J. S. New, J. P. Yevich and D. L. Temple, Jr.
CNS Research - Pharmaceutical Research and Development Division,
Bristol-Myers Company, Evansville, Indiana 47721

SUMMARY

Buspirone 1 is a novel, clinically effective anxiolytic agent which is devoid of the sedative, anticonvulsant or muscle relaxant properties normally associated with the benzodiazepines. Buspirone labelled with both radioactive (^{14}C) and stable (^{15}N) isotopes was required in order to investigate the metabolism of the compound. The synthesis of both labelled compounds beginning with either urea - ^{14}C or urea - $^{15}N_2$ is described.

Key Words: Buspirone, 2-chloropyrimidine

INTRODUCTION

The pursuit of nonbenzodiazepine anxiolytics has begun to witness the emergence of many structurally diverse candidates which claim to present fewer or less intense side effects in animals, compared to what is normally observed with the benzodiazepines. Buspirone is representative of this quest because it lacks the sedative, muscle relaxant or anticonvulsant effects which accompany the benzodiazepines.[1,2] Its anxiolytic activity is equipotent to that of diazepam but does not appear to be directly actuated through the benzodiazepine receptor.[3,4] Buspirone's mechanism of action has, therefore, been formulated as anxioselective. These observations emphasized the need for more detailed studies on the absorption and metabolic disposition of this compound.

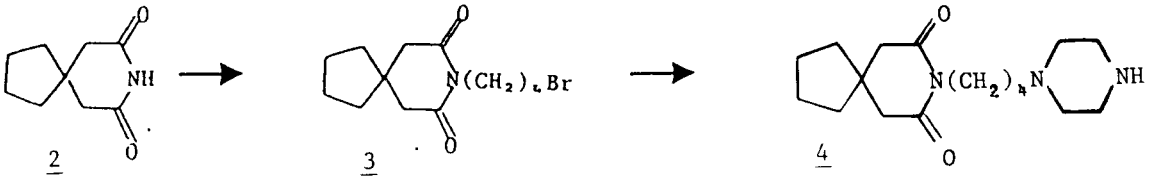
Earlier studies on the metabolism of this drug, involving tritiated compound obtained by exchange procedures, showed that this method led to ambiguity in interpretation of the results.[5] Therefore, a synthesis was devised which would allow incorporation of isotopes in positions which would be chemically and metabolically more secure. This scheme accommodated the labelling of buspirone in both radioactive (^{14}C) and stable isotope ($^{15}N_2$) form; the former for distribution studies and the latter for use in conjunction with GC/MS analysis.

0362-4803/83/101207-05$01.00

Received November 13, 1981
Revised July 11, 1983

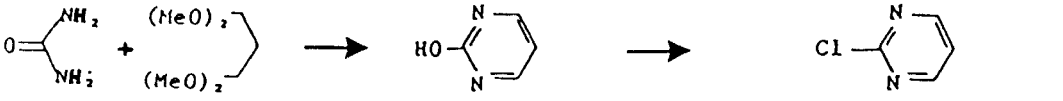
RESULTS AND DISCUSSION

Alkylation of 3,3-tetramethylene glutarimide 2 with 1,4-dibromobutane in toluene afforded 3 which was purified by distillation under reduced pressure. The conversion of 3 to 4 was accomplished with excess piperazine in refluxing toluene producing a 42% yield of product. The availability of urea



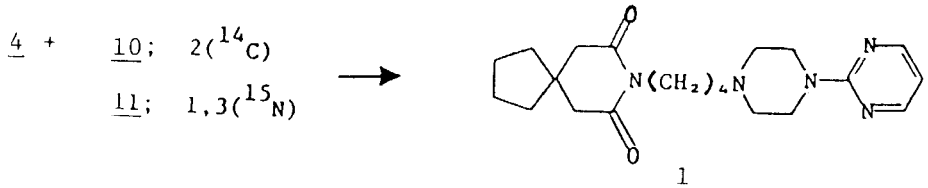
2 3 4

labelled on carbon with ^{14}C (5) and on nitrogen with $^{15}N_2$ (6) allowed us to employ one of the classic schemes for the preparation of pyrimidines. Acid catalyzed condensation of each urea with malondialdehyde 7 yielded the corresponding pyrimidinols (8,9). These derivatives were simply converted to their chlorinated analogues 10 and 11, by means of $POCl_3$.



5 ^{14}C
6 ^{15}N
7
8 2(^{14}C)
9 1.3(^{15}N)
10 2(^{14}C)
11 1.3(^{15}N)

The sequence was completed by alkylation of 4 with the appropriate 2-chloropyrimidines 10 and 11, affording 12 and 13 in overall yields of 22% and 38%, respectively. Both CI and EI mass spectroscopy indicate that 75% of 13 contains ^{15}N at both N_1 and N_3; a minor fraction (4%) contains only one ^{15}N while approximately 20% of the material contains no label.



4 + 10; 2(^{14}C)
11; 1.3(^{15}N)

1
12 (^{14}C)
13 (^{15}N)

EXPERIMENTAL

The products were characterized by their chromatographic properties, melting points and spectral analyses. Precoated

TLC plates (Silica Gel 60 F-254) were used in the solvent systems indicated. NMR spectra (90 MHz) were recorded on a Perkin Elmer R-32 spectrometer. A Beckman IR9 spectrophotometer was used for infrared analyses. Radiolabelled solutions were counted using a Beckman LS 335 liquid scintillation spectrometer. Mass spectral analyses were carried out using a Finnigan 4000 EI-CI mass spectrometer.

8-(4-Bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (3). A mixture of 3,3-tetramethylene glutarimide (33.4 g, 0.2 mol), 1,4-dibromobutane (86.4 g, 0.4 mol), and K_2CO_3 (88.6 g, 0.6 mol) (micropulverized) in 500 ml of dry toluene was stirred at reflux for 20 hr. The reaction mixture was filtered while hot and concentrated in vacuo; the residual oil collected was distilled under reduced pressure. The fraction b.p. 165-170°C (0.1 mm Hg), was collected to afford 32.0 g (52%) of an oil whose spectral properties were consistent with the structure. IR (neat): 2950, 2860, 1725, 1670, 1430, 1390, 1350, 1130, cm^{-1}; NMR ($CDCl_3$): δ = 1.68 (m, 12H); 2.59 (S, 4H); 3.40 (t, 2H, J = 6.2 Hz); 3.78 ppm (t, 2H, J = 6.6 Hz)

8-[4-(1-Piperazinyl)butyl-8-azaspiro[4.5]decane-7,9-dione (4). A mixture of 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (32.0 g, 0.11 mol), piperazine (50 g, 0.58 mol), and K_2CO_3 (80.0 g, 0.58 mol) (micropulverized) in 500 ml of dry toluene was stirred at reflux for 18 hr. The reaction mixture was filtered while hot and concentrated under reduced pressure; the residual oil collected was mixed with 100 ml of Et_2O, and the excess piperazine which precipitated was removed by filtration. The filtrate was concentrated in vacuo to an oil, and distilled under vacuum, yielding a fraction (180 - 200°C/0.1 mmHg), which amounted to 13.5 g (42%) of product. This oil was dissolved in 40 ml of EtOH and treated with 15 ml of 7N ethanolic HCl; cooling led to crystallization of the white dihydrochloride salt; m.p. 235 - 237°C: IR (0.5% KBr): 2960, 2710, 2560, 1720, 1670, 1430, 1400, 1350, 1125 cm^{-1}; NMR (DMSO·d_6): δ = 1.54 (m, 12H); 2.64 (S, 4H); 3.12 (m, 2H); 3.47 (m, 8H); 3.65 (t, 2H, J = 6.6 Hz); 10.50 ppm (br.s., 2H) Anal. Calc'd for $C_{17}H_{19}N_3O_2$·2HCL·0.25 H_2O: C, 53.06; H, 8.25; N, 10.92. Found C, 53.06; H, 8.05; N, 10.96.

2-Hydroxypyrimidine-2-^{14}C Hydrochloride (8). A solution of urea (122 mg, 2.7 mmol), urea ^{14}C (43 mg, 0.7 mmol, 30 mCi), and of malonaldehyde bis (dimethylacetal) (443 mg, 2.7 mmol) in 1.0 ml ethanol was treated with 0.5 ml conc. HCl. The solution was warmed on a steam bath for 2 hr, chilled and seeded to give a yellow precipitate. The product was collected on a filter to afford 274 mg (75%) of solid. This crude material was used without further purification.

2-Chloropyrimidine-2-^{14}C (10). The crude hydroxypyrimidine·HCl (274 mg, 2.06 mmol), was treated with 10 ml of $POCl_3$. The mixture was heated to 110°C in an oil bath with stirring for 6 hr. Excess $POCl_3$ was removed in vacuo and the residual oil dissolved in 15 ml of water. The aqueous solution was treated with 10% $NaHCO_3$ until slightly basic, extracted into chloroform, dried (Na_2SO_4), and filtered. Concentration in vacuo provided 190 mg (81%) of crude -2-chloropyrimidine-2-^{14}C which was used in the next step without further purification.

Buspirone-^{14}C (12). The crude 2-chloropyrimidine-2-^{14}C (190 mg, 1.6 mmol), 8-[4-(1-piperazinyl)butyl]-8-azaspiro[4.5]decane-7,9-dione (4) (509 mg, 16 mmol), and

triethylamine (162 mg, 1.6 mmol) in 15 ml of EtOH was sealed in a Parr bomb and heated in an oil bath at 110 - 120°C for 3 days. The solution was then cooled, concentrated, and the residual oil taken up in 10 ml of i-PrOH. This solution was treated with 0.23 ml of 7N ethanolic HCl, which upon cooling led to crystallization of the hydrochloride salt. This crude material was recrystallized from i-PrOH affording 281 mg (42%) of product. The salt was dissolved in water and $NaHCO_3$ added with cooling until the mixture was just basic. The precipitate was collected on a filter and recrystallized from i-PrOH to give 125 mg (35%) of product. The compound was shown to be radiochemically pure using TLC. The strips were developed in two separate solvent systems [$CHCl_3$ - EtOH (4:1) and $CHCl_3$ - MeOH-HOAC (10:3:1)] and scanned with a Varian Aerograph-Berthold Radioscanner. Samples were counted and the specific activity was found to be 7.6 mCi/mmol; m.p. 101 - 102°C: IR (0.5% KBr): 2960, 1720, 1670, 1580, 1550, 1500, 1450, 1360, 1260, 1130, 980, 800 cm^{-1}; NMR ($CDCl_3$): δ = 1.58 (m, 12H); 2.46 (m, 6H); 2.57 (s, 4H); 3.81 (m, 6H); 6.41 (t, 1H, J = 4.8 Hz); 8.25 ppm (d, 2H, J = 4.8 Hz). Anal. Calc'd. for $C_{21}H_{31}N_5O_2$: C, 65.43; H, 8.11; N, 18.17. Found: C, 65.60; H, 8.10; N, 18.24.

2-Hydroxypyrimidine-1,3-^{15}N (9). A solution of urea - $^{15}N_2$ (3.0 g, 0.049 mol) (90 atom % ^{15}N), and of malonaldehyde bis (dimethylacetal) (8.2 g, 0.049 mol) in 10 ml of EtOH was treated with 10 ml conc.HCl. The solution was warmed on a steam bath for 2 hr., chilled and seeded to give a yellow precipitate. This was collected on a filter to give 5.1 g (80%) of product, m.p. 210 - 212°C. This material was used without further purification or analysis in the next step.

2-Chloropyrimidine-1,3-^{15}N (11). The crude hydroxypyrimidine 9 (5.1 g, 0.038 mol) was suspended in 30 ml of $POCl_3$ and heated at 110°C with stirring for 6 hr. The excess $POCl_3$ was removed under reduced pressure and the residual oil dissolved in 15 ml of H_2O. The aqueous solution was made alkaline with 10% $NaHCO_3$, extracted with $CHCl_3$, and the organic phase dried (Na_2SO_4), filtered, and concentrated in vacuo yielding 3.0 g (68%) of 2-chloropyrimidine-1,3-^{15}N, m.p. 66-68°C. This material was used without further purification in the next step.

Buspirone - $^{15}N_2$ (13). The crude 2-chloropyrimidine (11) (3.0 g, 0.026 mol), 8-[4-(1-piperazinyl)butyl]-8-azaspiro [4.5]-decane-7,9-dione (4) (18.07 g, 0.026 mol), and triethylamine (2.6 g, 0.026 mol), in 25 ml of EtOH was sealed in a Parr bomb and heated in an oil bath at 110 - 120°C for 72 hr. The solution was cooled, concentrated in vacuo and the residual oil taken up in hot i-PrOH. The solid which separated on cooling was collected on a filter to afford 7.0 g (70%) of product, m.p. 101-102°C. This material was converted to its hydrochloride salt with one equivalent of conc.HCl in i-PrOH to give white crystals, m.p. 185-186°C; IR (0.5% KBr): 2965, 2480, 1730, 1680, 1580, 1490, 1450, 1365, 1130, 970 cm^{-1}; NMR ($CDCl_3$): δ = 1.65 (m, 12H); 2.62 (s, 4H); 3.02 (m, 4H); 3.78 (m, 6H); 5.82 (m, 2H); 6.58 (t, 1H, J = 4.8 Hz); 8.33 (dd, 2H, J = 4.8 Hz and 11.0 Hz); 12.90 ppm (br.s, 1H); ^{13}C-NMR

($CDCl_3$-free base): δ = 22.63, 24.21, 25.65, 37.60, 38.69, 39.50, 42.34, 44.92, 52.50, 57.76, 110.47 (t, ^2J ^{13}C - ^{15}N = 2.4 Hz), 157.80 (d, ^1J ^{13}C-^{15}N = 4.0 Hz). Anal. Calc'd. for $C_{21}H_{31}N_5O_2 \cdot HCl$: C, 59.55; H, 7.61; N, 16.91. Found: C, 59.73; H, 7.60; N, 16.54.

1. Temple, D. L., Yevich, J. P. and New, J. S. - J. Clin. Psychiat. 43: 4 (1982).

2. Yevich, J. P., Temple, D. L., New, J. S., Taylor, D. P. and Riblet, L. A. - J. Med. Chem. 28: 194 (1982).

3. Riblet, L. A., Taylor, D. P., Eison, M. S. and Stanton, H. C. - J. Clin. Psychiatry 43: 12 (1982).

4. Goldberg, H. L. and Finnerty, R. J. - Am. J. Psychiatry 136: 1184 (1979).

5. British Patent 663,302, December 19, 1951.