SYNTHESIS OF DEUTERIUM-LABELLED PEPTIDO-AMINOBENZOPHENONE [4-CHLORO-2-(2'-CHLOROBENZOYL)-N-(GLYCYLGLYCYL)-N-METHYL-ANILIDE] AND ITS METABOLITES

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SUMMARY

Deuterium-labelled peptido-aminobenzophenone [4-chloro-2-(2'-chlorobenzoyl)-N-(glycylglycl)-N-methylanilide, 1] and its benzodiazepine-metabolites were prepared for use as internal standards in the quantification of the peptido-aminobenzophenone, chlorodiazepam, lormetazepam, chlorodesmethyldiazepam, and lorazepam at low levels in human plasma by selected ion monitoring.

Key Words: Deuterium Labelling, Synthesis, Benzodiazepines

INTRODUCTION

The peptido-aminobenzophenone, 4-chloro-2-(2'-chlorobenzoyl)-N-(glycylglycyl)-N-methylanilide (1), was developed as a potent minor tranquilizer in our laboratory.[1] Its metabolism to the corresponding benzodiazepines has been studied with rats[2] and dogs[3] (Fig. 1). Lahti *et al.*[4] and Rising *et al.*[5] reported that N-alkylaminoacetamidobenzophenone undergoes N-dealkylation followed by ring closure *in vivo* to give the corresponding benzodiazepines.

This paper reports the synthesis of deuterium-labelled peptido-aminobenzophenone, its thermally stable derivative, and its metabolites for use as internal standards in the quantification of 1, chlorodiazepam (2), lormetazepam (3), chlorodesmethyl-

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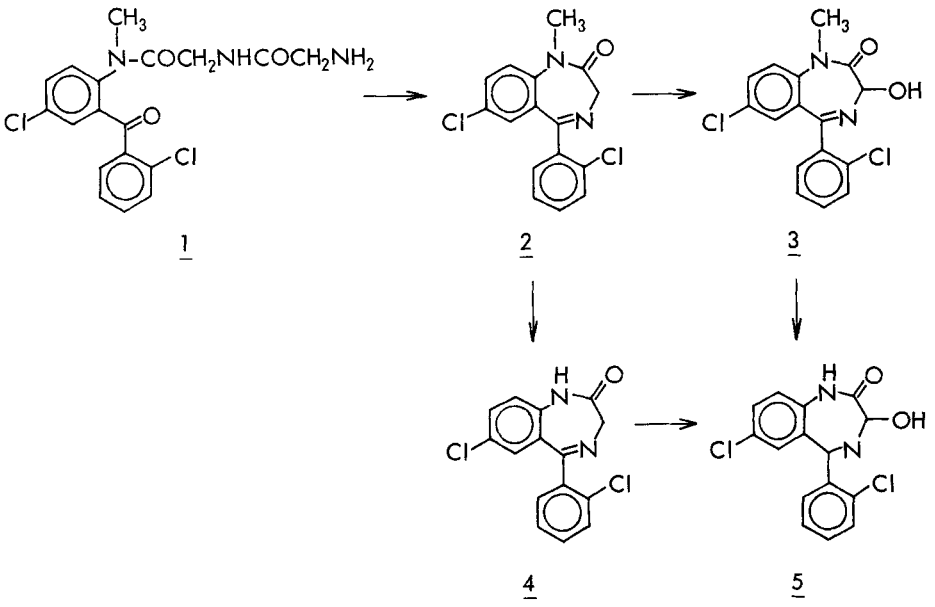

Fig. 1. Postulated metabolic pathways of peptido-amino-benzophenone (1).

diazepam (4), and lorazepam (5) in human plasma by gas chromatography-mass spectrometry.[6] The synthetic routes of these compounds are shown in Figure 2.

RESULTS AND DISCUSSION

This paper describes the synthesis of isotopically pure deuterium-labelled compounds containing three deuterium atoms on the N-methyl group or four deuterium atoms on the benzene ring. The reaction pathways for preparing (8), (9), (17), (20), (23), (24), (26) and (27) are shown in Figure 2. The source of deuterium was methyl iodide-d_3 or toluene-d_8.

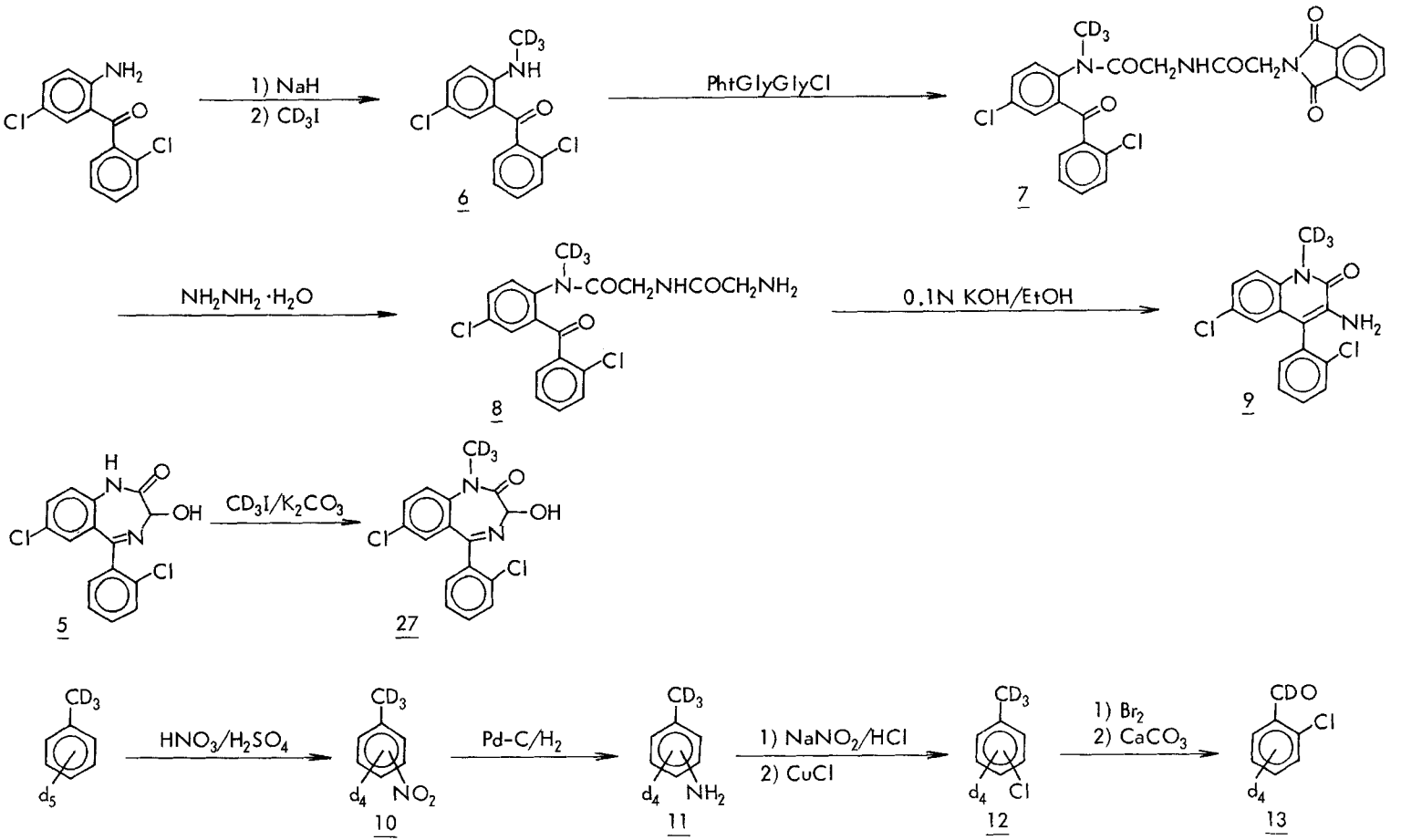

Fig. 2. Synthetic route of deuterium-labelled peptido-aminobenzophenone (1) and its metabolites.

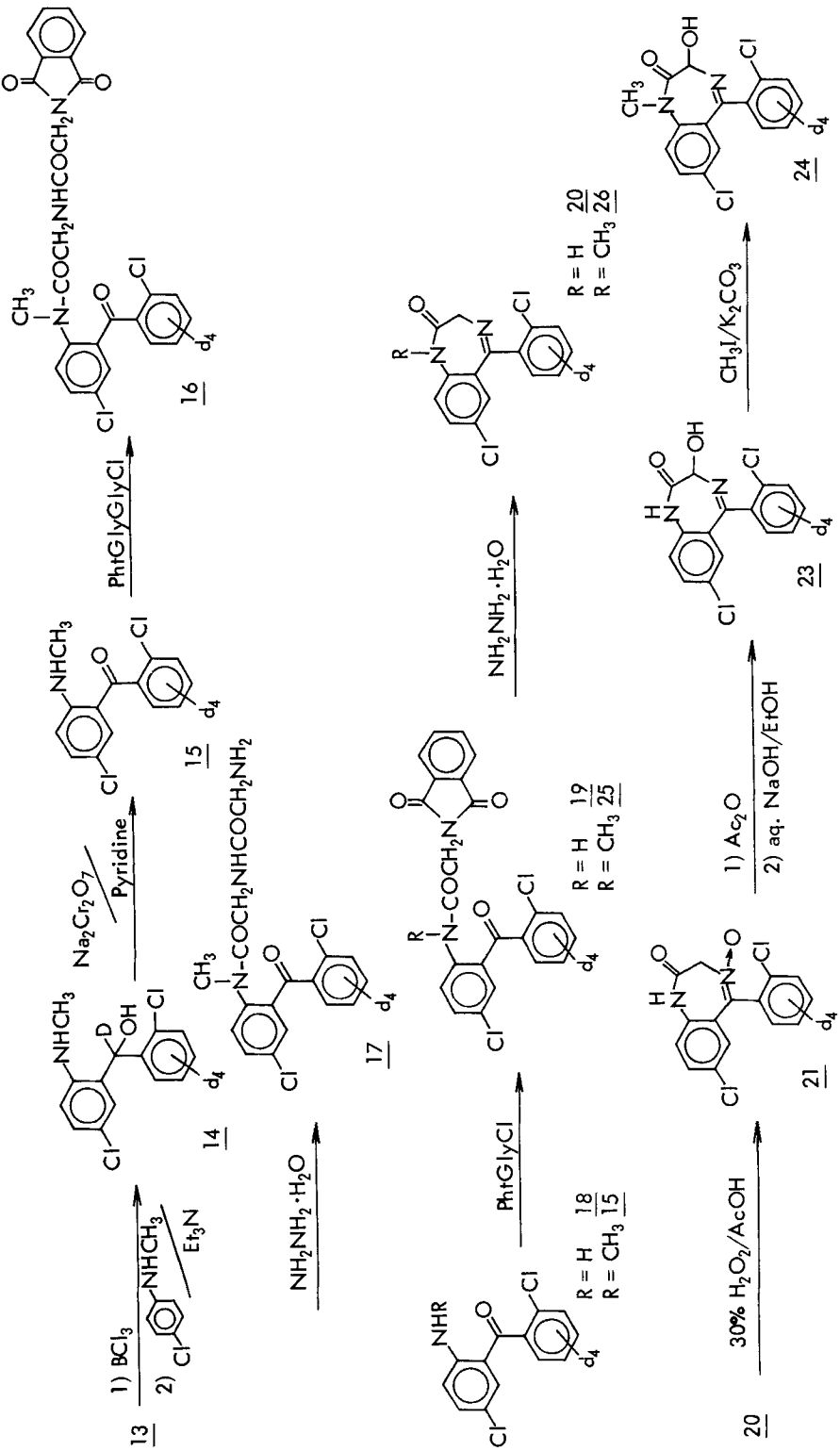

Fig. 2 (continued)

Derivation from CD_3I

The deuteriomethyl compound, 2',5-dichloro-2-(N-methylamino-d_3)benzophenone (6), was obtained by methylation of 2-amino-2',5-dichlorobenzophenone with methyl iodide-d_3.[11] The coupling reaction of 6 with phthaloylglycylglycyl chloride[14] in benzene gave the 4-chloro-2-(2'-chlorobenzoyl)-N-(phthaloylglycylglycyl)-N-(methyl-d_3)anilide (7) in good yield. Hydrazinolysis of the phthaloyl group in 7 gave 4-chloro-2-(2'-chlorobenzoyl)-N-(glycylglycyl)-N-(methyl-d_3)anilide (8). The reaction of 8 with 0.1 N KOH in EtOH gave 3-amino-6-chloro-4-(2'-chlorophenyl)-1-(methyl-d_3)-2(1H)quinoline-2-one (9) in good yield. As compound 8 gave a few peaks due to thermal decomposition on GLC, it was converted into the thermally stable compound 9.[8] Lormetazepam-d_3, 7-chloro-5-(2'-chlorophenyl)-1,3-dihydro-3-hydroxy-1-(methyl-d_3)-2H-1,4-benzodiazepin-2-one (27), was obtained from lorazepam (5) by the reaction with CD_3I and K_2CO_3 in dry DMF at room temperature in good yield.

Derivation from toluene-d_8

The key intermediates in the preparation of the desired 4-chloro-2-(2'-chlorobenzoyl-d_4)-N-(glycylglycyl)-N-methylanilide (17) and [5-(2'-chlorophenyl-d_4)]benzodiazepines [(20), (23), (24) and (26)] were 2-amino-2',5-dichlorobenzophenone-3',4',5',6'-d_4 (18) and its 2-methyl derivative (15), which were synthesized by a reaction sequence starting from toluene-d_8.

o-Chlorobenzaldehyde-d_5 (13) was synthesized *via* several steps from toluene-d_8. Nitration of toluene gave a mixture of o- and p-isomers. Separation of the mixture was carried out at the chlorobenzaldehyde step, because easier separation and higher yield were attained than at other steps. The o- and p-chlorobenzaldehydes were produced in the ratio of *ca*. 5:1 according to GLC determination. The coupling reaction of 13 with p-chloro-N-

methylaniline in the presence of BCl_3 under the conditions reported by Sugasawa et al.[9] gave 4-chloro-2-[α-hydroxy-2'-chlorobenzyl-d_5]-N-methylaniline (14).

Aminobenzhydrol (14) was oxidized with $Na_2Cr_2O_7$ in pyridine and gave the 2',5-dichloro-2-methylaminobenzophenone-3',4',5',6'-d_4 (15). Hydrazinolysis of the phthaloyl group in 4-chloro-2-(2'-chlorobenzoyl-d_4)-N-(phthaloylglycyl)anilide (19) and 4-chloro-2-(2'-chlorobenzoyl-d_4)-N-(phthaloylglycyl)-N-methylanilide (25) gave N-glycylaminobenzophenones which cyclized spontaneously to 1,4-benzodiazepinones, 7-chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (20) and 7-chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one (26), respectively.[7]

N-Oxidation of 20 with 30% H_2O_2 in AcOH led to 7-chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-2H-1,4-benzodiazepin-2-one-4-oxide (21) in 61% yield. The preparation of 7-chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one (23) was employed for the Polonovski rearrangement of the N-4-oxide (21), and the resulting 3-acetoxy-7-chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (22) was hydrolyzed in alkaline medium.[10]

Lormetazepam-d_4, 7-chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-3-hydroxy-1-methyl-2H-1,4-benzodiazepin-2-one (24) was obtained from 23 by the same procedure as for the synthesis of lormetazepam-d_3 (27).

EXPERIMENTAL

All melting points were measured on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60A spectrometer. Mass spectra were measured using a Hitachi RMU-6E spectrometer. The isotopic purity of each deuterium-labelled compound was determined by comparison of its

mass spectrum with the corresponding spectrum of the unlabelled compound. Column chromatography was carried out with silica gel (0.063-0.2 mm; Merck A.G., Darmstadt, G.F.R.).

2',5-Dichloro-2-(N-methylamino-d_3)benzophenone (6). To a suspension of NaH (1.32 g; 27.5 mmol of a 50% mineral oil suspension, practical grade; Wako Pure Chemical Industries Ltd., Osaka, Japan) in dry DMF (7 ml) was added a solution of 2-amino-2',5-dichlorobenzophenone (7.3 g, 27.5 mmol; Aldrich, Milwaukee, Wisc., U.S.A.) in dry DMF (16 ml) at 0° over a period of 0.5 hr. This was maintained at room temperature for 1 hr, then a solution of methyl iodide-d_3 (2.1 ml, 33 mmol; E. Merck, Darmstadt, G.F.R.) in dry DMF (8.5 ml) was added at 0° with stirring over 20 min. After stirring for an additional 1.5 hr at 0°, the reaction mixture was diluted with H_2O (35 ml), then neutralized with 2 N HCl to separate an oily substance. The separated oil was extracted with benzene (50 ml, 20 ml x 2). The benzene layer, after being washed with H_2O and dried over Na_2SO_4, was evaporated, leaving a yellow solid (8.6 g). Recrystallization from hexane gave yellow prisms (6.0 g; 77%), mp 87-88° (lit.[15] mp for the unlabelled compound 88-90°); NMR: δ 8.76 (s br, 1 H, ArNH); 6.60-7.42 (7 H, overlapping multiplets). Anal. Calcd. for $C_{14}H_8D_3Cl_2NO$: C, 59.38; H, 2.85; D, 2.14; N, 4.95. Found: C, 59.46; H, 2.79; D, 2.09; N, 4.98. The isotopic composition was 99.5% d_3 and 0.5% d_2.

4-Chloro-2-(2'-chlorobenzoyl)-N-(phthaloylglycylglycyl)-N-(methyl-d_3)anilide (7). This compound was prepared from 6 by the same procedure as for the synthesis of the unlabelled compound described by Hirai et al.[7] The crude product (7) was used for the following reaction without purification.

4-Chloro-2-(2'-chlorobenzoyl)-N-(glycylglycyl)-N-(methyl-d_3)anilide (8). Using a procedure similar to that described for the synthesis of the unlabelled compound[7], compound 8 was

obtained from 6 in 61% yield. Recrystallization from isoPrOH-H_2O gave colorless scales, mp 82-85° (lit.[7] mp 95-100° for unlabelled compound); NMR: δ 7.83 (t br, J = 6 Hz, 1 H, $-CH_2N\underline{H}$); 7.12-7.68 (7 H, overlapping multiplets, Ar$\underline{H}$); 3.86 (d, J = 6 Hz, 2 H, $-C\underline{H}_2NH$); 3.34 (s br, 2 H, $-C\underline{H}_2NH_2$); 1.65 (s br, 2 H, $N\underline{H}_2$). Anal. Calcd. for $C_{18}H_{14}D_3N_3O_3Cl_2 \cdot H_2O$: C, 52.06; H, 3.88; D, 1.46; N, 10.12. Found: C, 52.23; H, 3.98; D, 1.49; N, 10.05.

3-Amino-6-chloro-4-(2'-chlorophenyl)-1-(methyl-d_3)-2(1H)-quinolin-2-one (9). A solution of 8 (0.30 g; 0.72 mmol) in 0.1% KOH-EtOH (10 ml; 1 mmol) was refluxed for 2.5 hr and then evaporated. Column chromatography of the residue with CH_2Cl_2 as an eluant gave 9 as colorless crystals (0.20 g, 85%). Recrystallization from benzene gave colorless prisms, mp 234-235°; NMR: δ 6.78-7.73 (overlapping multiplets, 7 H, Ar$\underline{H}$); 4.39 (s br, 2 H, $N\underline{H}_2$). Anal. Calcd. for $C_{16}H_9D_3N_2OCl_2$: C, 59.64; H, 2.82; D, 1.88; N, 8.69. Found: C, 59.92; H, 2.95; D, 1.96; N, 8.68. The isotopic composition was 99.1% d_3 and 0.9% d_2.

7-Chloro-5-(2'-chlorophenyl)-1,3-dihydro-3-hydroxy-1-(methyl-d_3)-2H-1,4-benzodiazepin-2-one (27). A mixture of lorazepam ($C_{15}H_{10}N_2O_2Cl_2 \cdot C_2H_5OH$, 5, 200 mg, 0.545 mmol), powd. K_2CO_3 (83 mg, 0.6 mmol) and methyl iodide-d_3 (173 μl, 2.73 mmol; E. Merck) in dry DMF (1 ml) was stirred for 1.5 hr at room temperature. The reaction mixture was acidified to approximately pH 3 with gl. AcOH (0.6 ml). The resulting tar crystallized on addition of H_2O (10 ml) with scratching. The crystals that precipitated were collected by filtration. Recrystallization from EtOH gave colorless prisms (130 mg, 71%), mp 208-210° (lit.[17] mp 205-207° for the unlabelled compound); NMR: δ 7.00-7.72 (overlapping multiplets, 7 H, Ar$\underline{H}$); 5.00 (d, J = 9 Hz, 1 H, $-\underset{\underset{OH}{|}}{C\underline{H}}$); 4.72 (d, J = 9 Hz, 1 H, $-\underset{\underset{\overline{OH}}{|}}{CH}$). Anal. Calcd. for $C_{16}H_9D_3N_2O_2Cl_2$: C, 56.82; H, 2.68; D, 1.79; N, 8.28. Found: C,

56.90; H, 2.68; D, 1.78; N, 8.24. The isotopic composition was 99.1% d_3 and 0.9% d_2.

2',5-Dichloro-2-methylaminobenzophenone-3',4',5',6'-d_4 (15).

Nitration of Toluene-d_8. To a mixture of $^cH_2SO_4$ (12.8 g; 0.13 mol) and 60% HNO_3 (d = 1.38, 10 g; 0.26 mol) was added toluene-d_8 (10 g; 0.1 mol; 99.7% isotopic purity; E. Merck) dropwise at 25-30° over 1 hr, and the resulting solution was stirred at the same temperature for 1.5 hr. H_2O was added to the solution and extracted with CH_2Cl_2 (30 ml x 2). The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated. The residual oil was distilled at 64-66° under diminished pressure (0.3 mmHg). Yield, 10 g (73%).

Reduction of Nitrotoluene-d_7. A solution of a mixture of o-and p-nitrotoluene-d_7 (10, 16.5 g) in EtOH (110 ml) was shaken in H_2 atmosphere over 5% Pd-C (700 mg). When H_2 gas of 1.1 times of theoretical amount had been absorbed, the reaction was stopped. The catalyst was removed by filtration, and the filtrate was evaporated, giving 11: Yield, 12.8 g (98%). The crude product 11 was used for the following reaction without purification.

Sandmeyer Reaction of Toluidine-d_7. To a suspension of the mixture of o- and p-toluidine-d_7 (11, 13 g; 0.11 mol) in 28% HCl (70 ml) was added dropwise a solution of $NaNO_2$ (8.3 g; 0.12 mol) in H_2O (23 ml) with stirring at 0-5°. To a solution of freshly prepared CuCl[12] in 28% HCl (70 ml) was added the above diazonium solution at a time under ice cooling. The reaction mixture was allowed to stand at room temperature for 1.5 hr with stirring and then extracted with CH_2Cl_2. Distillation of the extract yielded 12. Bp 140-150°. Yield 11.5 g (75%).

o-Chlorobenzaldehyde-d_5 (13). Under illumination with a 300-watt tungsten lamp, Br_2 (13.9 ml; 0.28 mol) was added slowly to a mixture of o- and p-chlorotoluene-d_7 (12, 11.5 g; 86.0 mmol) with stirring at 105°. About half of the Br_2 was added over an

hour with the temperature kept at 105-110°. When Br_2 color disappeared, the rest was added over one hour with the temperature maintained at 135°. This temperature was maintained for an additional hour. The crude chlorobenzal bromide was mixed thoroughly with powdered $CaCO_3$ (32.8 g; 0.33 mol). H_2O (44 ml) was added, then the mixture was refluxed for 15 hr. The product was distilled in a current of steam. The distillate was extracted with CH_2Cl_2, then CH_2Cl_2 extract was washed with H_2O, dried over Na_2SO_4, and evaporated. Preparative gas-chromatographic separation of the products (11.3 g) [Instrument: Varian 1520-1B, column: 10% carbowax-20M on chromosorb W 60-80 mesh (3/8" I.D. x 10'), column temperature: 190°, injector temperature: 250°, detector temperature: 220°, carrier gas: He 150 ml/min, detector: TCD] was carried out twice and afforded o-chlorobenzaldehyde-d_5 (13) as a colorless oil (3.15 g, 25%, isomeric purity >99%).

4-Chloro-2-[α-hydroxy-2'-chlorobenzyl-d_5]-N-methylaniline (14). This compound was prepared from 13 and 4-chloro-N-methylaniline in 78% yield by the same procedure as for the synthesis of the unlabelled compound.[9] Recrystallization from cyclohexane gave colorless plates, mp 110-111° (lit.[9] mp for the unlabelled compound 106-108°); NMR: δ 6.53-7.27 (overlapping multiplets, 3 H, ArH); 3.30 (s br, 2 H, NH & OH); 2.84 (s, 3 H, N-CH_3). Anal. Calcd. for $C_{14}H_8D_5NOCl_2$: C, 58.55; H, 2.81; D, 3.51; N, 4.88. Found: C, 58.64; H, 2.86; D, 3.55; N, 4.92.

2',5-Dichloro-2-methylaminobenzophenone-3',4',5',6'-d_4 (15).[13] To a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (4.2 g; 14 mmol) in ^cHCl (2.3 ml) and pyridine (60 ml) was added a solution of the benzhydrol 14 (1.93 g; 6.75 mmol) in pyridine (20 ml) with stirring at 10° over 10 min, and the mixture was allowed to stand at room temperature for 3 hr. The reaction mixture was poured into ice water (300 ml) to separate an oily substance which was extracted

with ether. The organic layer was washed with H_2O, dried over K_2CO_3, and evaporated. Chromatography of the residue on a silica gel column with CCl_4-$CHCl_3$ (3:2, v/v) gave 15 (800 mg; 42%) and further chromatography with the same solvent systems gave 18 (400 mg; 22%). NMR (15): δ 6.64-7.43 (3 H, overlapping multiplets, ArH); 3.00 (d, J = 5 Hz, 3 H, -NHCH$_3$).

4-Chloro-2-(2'-chlorobenzoyl-d_4)-N-(phthaloylglycylglycyl)-N-methylanilide (16). This compound was synthesized from 15 and phthaloylglycylglycyl chloride[14] in quantitative yield by the same procedure as that for the synthesis of the unlabelled compound.[7]

4-Chloro-2-(2'-chlorobenzoyl-d_4)-N-(glycylglycyl)-N-methylanilide (17). Hydrazinolysis of 16 was carried out in 82% yield by the same procedure as that described above for the preparation of 8 from 7.[7] Recrystallization from isoPrOH-H_2O gave colorless scales, mp 82-84° (lit.[7] mp 95-100° for the unlabelled compound). Anal. Calcd. for $C_{18}H_{13}D_4N_3O_3Cl_2 \cdot H_2O$: C, 51.93; H, 3.63; D, 1.94; N, 10.09. Found: C, 51.97; H, 3.65; D, 1.93; N, 9.94. The isotopic composition was 96.1% d_4, 3.2% d_3 and 0.7% d_2.

4-Chloro-2-(2'-chlorobenzoyl-d_4)-N-(phthaloylglycyl)anilide (19). This compound was synthesized from 2-amino-2',5-dichlorobenzophenone-3',4',5',6'-d_4 and phthaloylglycyl chloride in quantitative yield by the same procedure described above for the preparation of 7 from 6.[7] The crude product 19 was used for the following reaction without purification.

7-Chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (20). Hydrazinolysis of 19 was carried out in 90% yield by the same procedure described above for the preparation of 8 from 7.[7] Recrystallization from isoPrOH gave colorless prisms, mp 141-143° (lit.[16] mp 135-136° for unlabelled compound). Anal. Calcd. for $C_{15}H_6D_4N_2OCl_2$: C, 58.27; H, 1.96; D, 2.61; N, 9.06. Found: C, 58.28; H, 1.83; D, 2.50; N, 9.14. The

isotopic composition was 98.2% d_4, 1.5% d_3 and 0.3% d_2.

7-Chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-2H-1,4-benzodiazepin-2-one-4-oxide (21). A mixture of 20 (156 mg; 0.505 mmol) and 30% H_2O_2 (0.35 ml; 3.42 mmol) in gl. AcOH (9.3 ml) was warmed at 70° for 15 hr with stirring. The solution was concentrated to about one third in vacuo and poured on cracked ice, then neutralized with aqueous Na_2CO_3. The precipitated crystals were collected by filtration and dried over P_2O_5 at 60° in vacuo. Yield, 100 mg (61%). The crude product 21 was used for the following reaction without purification.

3-Acetoxy-7-chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (22). This compound was prepared from 21 in 58% yield by the procedure described by Bell and Childress.[10] The crude product 22 was used for the following reaction without purification.

7-Chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one (23). This compound was prepared from 22 in 69% yield by the procedure described by Bell and Childress.[10] Recrystallization from EtOH gave colorless prisms, mp 165° (decomp.) (lit.[17] mp 166-168° for the unlabelled compound). Anal. Calcd. for $C_{15}H_6D_4N_2O_2Cl_2 \cdot 1/2C_2H_5OH$: C, 55.18; H, 2.61; D, 2.32; N, 8.05. Found: C, 55.59; H, 2.86; D, 2.54; N, 7.89. The isotopic composition was 97.5% d_4 and 2.5% d_3.

7-Chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-3-hydroxy-1-methyl-2H-1,4-benzodiazepin-2-one (24). A mixture of lorazepam-d_4 (23; 20 mg; 57.5 μmol), powd. K_2CO_3 (10 mg; 72.3 μmol) and methyl iodide (30 μl; 480 μmol) in dry DMF (150 μl) were stirred for 2 hr at room temperature. The reaction mixture was evaporated, then H_2O (2 ml) was added and evaporated. The residue was extracted with AcOEt (2 ml x 4). The AcOEt extract was dried over Na_2SO_4 and evaporated. Thin-layer chromatography of the residue with AcOEt then with ether gave 24 as colorless

crystals. Recrystallization from EtOH gave colorless prisms (6.5 mg; 33%), mp 205-207° (lit.[17] mp 205-207° for the unlabelled compound). Anal. Calcd. for $C_{16}H_8D_4N_2O_2Cl_2$: C, 56.65; H, 2.38; D, 2.38; N, 8.26. Found: C, 56.41; H, 2.29; D, 2.30; N, 8.16. The isotopic composition was 96.1% d_4 and 3.9% d_3.

4-Chloro-2-(2'-chlorobenzoyl-d_4)-N-(phthaloylglycyl)-N-methylanilide (25). This compound was synthesized from 15 and phthaloylglycyl chloride[14] in quantitative yield as described for the preparation of 7 from 6.

7-Chloro-5-(2'-chlorophenyl-d_4)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one (26). Hydrazinolysis of 25 was carried out in 90% yield as described above for the preparation of 8 from 7.[7]

Recrystallization from AcOEt-cyclohexane gave colorless plates, mp 209-210° (lit.[16] mp 199-201° for the unlabelled compound). Anal. Calcd. for $C_{16}H_8D_4N_2OCl_2$: C, 59.46; H, 2.50; D, 2.50; N, 8.67. Found: C, 59.45; H, 2.49; D, 2.47; N, 8.56. The isotopic composition was 96.9% d_4, 2.7% d_3 and 0.5% d_2.

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