Synthesis of 4-(2-Chlorophenyl)-1,6-dihydro-1,3,9-trimethylimidazo[1,2-a]pyrazolo[4,3-f][1,4]diazepine-9-^{14}C (CI-918-^{14}C)

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SUMMARY

4-(2-Chlorophenyl)-1,6-dihydro-1,3,9-trimethylimidazo[1,2-a]pyrazolo-[4,3-f][1,4]diazepine-9-^{14}C (CI-918-^{14}C) was made starting with acetyl-1-^{14}C chloride. An efficient synthesis of 1-chloro-2-propanone-2-^{14}C was developed as a precursor to 2-methyl-1,3-dioxolane-2-^{14}C-2-methanamine. The latter reacted with 4-(2-chlorophenyl)-1,6-dihydro-1,3-dimethylpyrazolo[3,4-e][1,4]diazepine-7-thione to yield 4-(2-chlorophenyl)-1,6-dihydro-1,3-dimethyl-N-[(2-methyl-1,3-dioxolan-2-yl-2-^{14}C)methyl]pyrazolo[3,4-e][1,4]diazepin-7-amine. Hydrolysis and cyclization gave the title compound. The six-step reaction sequence gave an overall radiochemical yield of 19%. The product had a specific activity of 8.31 mCi/mmol.

Keywords: 4-(2-Chlorophenyl)-1,6-dihydro-1,3,9-trimethylimidazo[1,2-a]-pyrazolo[4,3-f][1,4]diazepine-9-^{14}C, CI-918-^{14}C, 1-Chloro-2-propanone-2-^{14}C, 2-(2-Oxopropyl-2-^{14}C)-1H-isoindole-1,3(2H)-dione, 2-Methyl-1,3-dioxolane-2-^{14}C-2-methanamine, nonsedating anxiolytic

INTRODUCTION

4-(2-Chlorophenyl)-1,6-dihydro-1,3,9-trimethylimidazo[1,2-a]pyrazolo-[4,3-f][1,4]diazepine (CI-918) shows marked anxiolytic activity in the milk-drinking test in naive rats[1] and minimal sedative properties were observed. It was significantly less active than diazepam in a test for alcohol potentiation.[2] To facilitate the study of the metabolism and bioavailability of CI-918 it was necessary to synthesize the ^{14}C-labeled drug.

CI-918 was first synthesized by Butler.[3] An improved synthesis of CI-918 was developed in our Preparations Laboratory, which used 4-(2-chlorophenyl)-1,6-dihydro-1,3-dimethylpyrazolo[3,4-e][1,4]diazepine-7-thione (1) and

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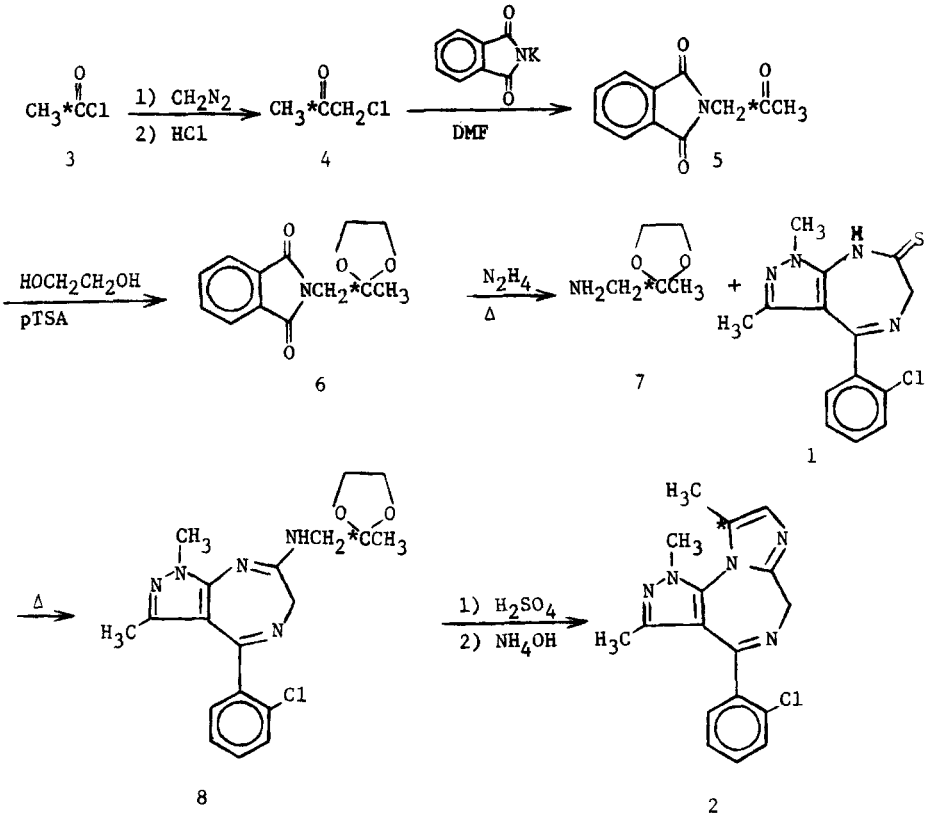
2-methyl-1,3-dioxolane-2-methanamine. A similar synthetic scheme has been reported in the preparation of some imidazobenzodiazepines.[4] 2-Methyl-1,3-dioxolane-2-methanamine was chosen to introduce a carbon-14 label (see scheme) into CI-918-^{14}C (2). An efficient method was developed to convert acetyl-1-^{14}C chloride (3) into 1-chloro-2-propanone-2-^{14}C (4).

RESULTS AND DISCUSSION

2-Methyl-1,3-dioxolane-2-methanamine, an intermediate in the CI-918 synthesis to be labeled with ^{14}C, was made using the Gabriel synthesis from 1-chloro-2-propanone. It was thus desirable to introduce the ^{14}C into 1-chloro-2-propanone.



3 4 5 6 7 1 8 2

(*-indicates locations of ^{14}C)

Reports of making α-halogenated ketones in the literature are numerous.[5] In most examples where 2-propanone was halogenated the ketone was used in large excess and mono- and disubstituted products resulted. The monosubstituted product was then isolated by fractional distillation. Of the numerous attempts to halogenate 2-propanone, bromination using phenyltrimethylammonium tribromide modified slightly from the procedure of Johnson, et al,[5c] gave the best results: product distribution of 86% 1-bromo-2-propanone, 8% 1,3-dibromo-2-propanone and 6% 1,1-dibromo-2-propanone as determined by ^{1}H-NMR of the crude product; 50% total yield. The isolation of monohalogenated product would be impractical on the scale required for ^{14}C-labeling work. This method and the others cited would not lend themselves to an efficient use of ^{14}C-labeled 2-propanone.

Another approach to synthesize 1-halo-2-propanone-2-^{14}C was desirable. The Nierenstein chloromethylation[6] appeared to be an acceptable alternative route to 1-chloro-2-propanone. Excess diazomethane in diethyl ether was treated with acetyl-1-^{14}C chloride (3) followed by the addition of HCl gas in diethyl ether to yield 4. Removal of HCl from the crude product 4 proved difficult. Unsubstituted phthalimide was formed instead of the desired 2-(2-oxopropyl-2-^{14}C)-1H-isoindole-1,3(2H)-dione (5), when the chloro compound 4, still containing HCl, was treated with potassium phthalimide. Atmospheric distillation and static vacuum transfer were only partially successful in removing the HCl. The addition of large amounts of inorganic bases was not effective either and isolation of 4 was hindered by the solid matrix. The addition of the non-nucleophilic base, N,N,N',N'-tetramethyl-1,8-naphthalenediamine (Proton Sponge®) in diethyl ether was effective at removal of HCl. Thus 4 was isolated free of HCl by static vacuum distillation in a 71% yield. 5 was produced by warming 4 with potassium phthalimide in N,N-dimethylformamide in an 83% yield after recrystallization. The ketal 2-[(2-methyl-1,3-dioxolan-2-yl-2-^{14}C)methyl]-1H-isoindole-1,3(2H)-dione (6) was made using 1,2-ethan-

ediol and a catalytic amount of 4-methylbenzenesulfonic acid in refluxing heptane in a 94% yield. Hydrazinolysis of 6 with anhydrous hydrazine in tetrahydrofuran afforded 2-methyl-1,3-dioxolane-2-^{14}C-2-methanamine (7) in a 75% yield.

1 and 7 were heated in refluxing tetrahydrofuran to give 4-(2-chlorophenyl)-1,6-dihydro-1,3-dimethyl-N-[(2-methyl-1,3-dioxolan-2-yl-2-^{14}C)-methyl]pyrazolo[3,4-e][1,4]diazepin-7-amine (8) in an 84% yield. Hydrolysis and cyclization was accomplished by treatment with concentrated sulfuric acid to give a 57% yield of 2 after recrystallization. The work up required the slow addition of the acid solution to cold ammonium hydroxide to prevent opening of the diazepine ring.

The overall yield of the six-step synthesis from acetyl-1-^{14}C chloride (3) was 19%. The chemical and radiochemical purity of 2 was >98% by TLC and HPLC. The IR and ^{1}H-NMR were identical to those of authentic unlabeled CI-918. The specific activity of 2 was found to be 8.31 mCi/mmol.

EXPERIMENTAL

Acetyl-1-^{14}C chloride (3) with a specific activity of 50 mCi/mmol was purchased from New England Nuclear Corporation. This was diluted with unlabeled acetyl chloride to a specific activity of 8.2 mCi/mmol. Diazald® and potassium phthalimide were purchased from Aldrich Chemical Company and 1,2-ethanediol was purchased from Mallinckrodt. 4-(2-Chlorophenyl)-1,6-dihydro-1,3-dimethylpyrazolo[3,4-e][1,4]diazepine-7-thione (1) was obtained from the Preparations Laboratory, Warner-Lambert/Parke-Davis, Ann Arbor, MI.

^{1}H-NMR spectra were determined on a Varian XL-200 FT NMR or Varian EM390 NMR spectrometer. Chemical shifts were reported in δ (ppm) downfield from tetramethylsilane. Infrared spectra were obtained on a Perkin Elmer 1430 ratio recording spectrophotometer or Nicolet MX-1/3600 FT-IR. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Liquid scintillation counting was done with a Packard 3320 liquid

scintillation counter using Beckman Ready-Solv MP liquid scintillation cocktail.

Thin layer chromatography (TLC) was done on EM Merck silica gel plates (250 μ). Radiochemical analysis of TLC plates was done with a Berthold 2832 Automatic TLC Linear Analyzer. High pressure liquid chromatography (HPLC) was performed using a Spectra Physics 8700 solvent delivery system, Kratos 773 UV detector at 280 nm, Hewlett-Packard 3390A Integrator and United Technologies Packard Tri-Carb RAM 7500 radioactivity monitor.

1-Chloro-2-propanone-2-^{14}C (4). Diazomethane was generated by adding Diazald (8.37 g, 35 mmol) in diethyl ether (50 mL) to a solution of potassium hydroxide (2.25 g), water (3.3 mL), and 2-(2-ethoxyethoxy)ethanol (12 mL). The diazomethane/diethyl ether solution was distilled using the Mini Diazald Apparatus (Aldrich Chemical Company). A solution of acetyl-1-^{14}C chloride (80 mCi, 1.6 mmol) and carrier acetyl chloride (645 mg, 8.2 mmol) in diethyl ether (3 mL) was added to the ice-cooled ethereal diazomethane solution. The solution was allowed to warm to room temperature with gas evolution noted. After 4.5 hours the reaction was cooled to 0°C and diethyl ether saturated with HCl (15 mL) was added. The reaction was allowed to warm to room temperature over 16 hours. Most of the diethyl ether was removed by atmospheric distillation.

A solution of N,N,N',N'-tetramethyl-1,8-napthalenediamine (1.0 g) in diethyl ether (1 mL) was added to remove excess HCl. The product was isolated as an ethereal solution by static vacuum transfer collecting 57 mCi (radiochemical yield 71%) of 4 at -200°C (liq N_2). This solution was used without characterization in the next step.

2-(2-Oxopropyl-2-^{14}C)-1H-isoindole-1,3(2H)-dione (5). A slurry of potassium phthalimide (1.48 g, 8.0 mmoles) in dry N,N-dimethylformamide (9 mL) was added to the 1-chloro-2-propanone-2-^{14}C solution from the previous step. The mixture was heated at 60°C for two hours under N_2. The cooling

water was removed from the condenser and the diethyl ether was allowed to distill. After an additional two hours at 60°C, the reaction was cooled. The solvent was removed by static vacuum transfer collecting the solvent at -200°C (liq N_2) while warming the reaction flask to 60°C. The resulting yellow solid was recrystallized from n-butanol to yield 1.168 g (5.75 mmol, 83% yield) of 5 as white needles: TLC R_f = 0.51 (EtOAc) >99% radiochemically pure; cochromatographed with an authentic unlabeled 5.

2-[(2-Methyl-1,3-dioxolan-2-yl-2-^{14}C)methyl]-1H-isoindole-1,3(2H)-dione (6). A mixture of 5 (1.168 g, 5.75 mmol), 1,2-ethandiol (353 µl, 6.32 mmol) and a trace of 4-methylbenzenesulfonic acid in heptane (15 mL) was placed in a flask fixed with a Dean-Stark trap and condenser. This was refluxed for five hours with removal of water. Upon cooling the product 6 (1.335 g, 94% yield) crystallized from solution: mp 84-90°C (mp of unlabeled reference material 84-91°C); TLC, R_f = 0.12 (CH_2Cl_2), cochromatographed with unlabeled material.

2-Methyl-1,3-dioxolane-2-^{14}C-2-methanamine (7). To a solution of 6 (1.335 g, 5.40 mmol, 42.5 mCi) in dry tetrahydrofuran (THF) (10 mL) under N_2, anhydrous hydrazine (377 µL, 11.9 mmol) was added. The solution was refluxed for 9.5 hours, forming a voluminous white precipitate. The reaction mixture was filtered, rinsing the isolated solid with additional THF (15 mL). The product and THF were codistilled from the filtrate by static vacuum distillation trapping the distillate at -200°C (liq. N_2) to recover 31.9 mCi (75% radiochemical yield) of 7: TLC, R_f = 0.25, 95% radiochemical purity (EtOAc: Et_3N 19:1); R_f = 0.40, 96% radiochemical purity (EtOAc:MeOH 1:1); cochromatographed with authentic unlabeled 2-methyl-1,3-dioxolane-2-methanamine.

4-(2-Chlorophenyl)-1,6-dihydro-1,3-dimethyl-N-[(2-methyl-1,3-dioxolan-2-yl-2-^{14}C)methyl]pyrazolo[3,4-e][1,4]diazepin-7-amine (8). To 1 (1.25 g, 4.10 mmol) was added the solution of 7 (31.9 mCi) in THF from the previous reaction. The orange slurry was heated to reflux. Gas evolution was noted and

a red solution resulted. After three hours, additional 1 (100 mg) was added with gas evolution noted. After one more hour, the reaction was cooled and the THF was removed in vacuo. The resulting foam was crystallized from ethyl acetate and filtered, rinsing with ethyl acetate. The volume of the filtrate was reduced and a second crop isolated. The combined tan material 8 was 1.269 g (84% yield): mp 205-207°C; TLC, R_f = 0.24, 91% radiochemical purity (EtOAc:Et_2NH 100:1); IR (KBr) 3240, 3060, 1605, 1500, 1190, 1062, 748, and 768 cm^{-1}, identical with unlabeled material.

4-(2-Chlorophenyl)-1,6-dihydro-1,3,9-trimethylimidazo[1,2-a]pyrazolo-[4,3-f][1,4]diazepine-9-^{14}C, CI-918-^{14}C (2). 8 (1.26 g, 3.24 mmol) was added to concentrated sulfuric acid (5.0 mL) over 20 minutes. The solution was heated at 60°C for 17 hours. After cooling, the acid solution was added to a well-stirred suspension of concentrated ammonium hydroxide (18 mL), CH_2Cl_2 (40 mL) and ice. The layers were separated. The aqueous layer was washed with CH_2Cl_2. The combined CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated in vacuo to a yellow foam. Crystallization from acetonitrile and drying at 80°C in vacuo afforded 602.7 mg (15.4 mCi, 57% yield) of off white 2: mp 201-202°C; specific activity 8.31 mCi/mmol; TLC, R_f = 0.22 (EtOAc:MeOH:Et_3N 8:2:0.1); R_f = 0.11 (EtOAc:EtOH 4:1), R_f = 0.57 ($CHCl_3$:EtOH:NH_4OH 1:1:0.01); HPLC: retention time 4.05 minutes, chemical and radiochemical purity >98%, Alltech silica gel, 10 μ, 4.6 mm ID x 25 cm, CH_2Cl_2:MeOH:NH_4OH 95:5:0.5, flow rate 2.0 mL/min; IR (KBr) 1595, 1512, 1420, 1060, 1000, and 770 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.35 (m, 4, ArH), 6.92 (s, 1, 8-CH), 5.37 (d, 1, J = 13 Hz, 6-CH_2), 4.11 (d, 1, J = 13Hz, 6-CH), 3.88 (s, 3, 1-CH_3), 2.36 (s, 3, 9-CH_3), 1.75 (s, 3, 3-CH_3). Both spectra were identical with those of an unlabeled standard. Anal. Calcd for $C_{17}H_{16}N_5Cl$: C, 62.67; H, 4.95; N, 21.50. Found: C, 62.60; H, 4.90; N, 21.46.

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