SYNTHESIS OF ^{14}C- AND ^{3}H-LABELED CI-911 (DIHYDRO-1H-PYRROLIZINE-3,5(2H,6H)-DIONE)

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SUMMARY

CI-911 [dihydro-1H-pyrrolizine-3,5(2H,6H)-dione] (1), a new cognition activating agent, was radiolabeled with ^{14}C and ^{3}H. The ^{14}C-labeled synthesis was accomplished using nitromethane-^{14}C as the starting material to result in an overall radiochemical yield of 9.2%. The ^{3}H-labeled CI-911 was synthesized with a specific activity of 28.1 Ci/mmol by catalytic tritium reduction of 3-(5-oxo-2-pyrrolidinyl)-2-propenoic acid, phenylmethyl ester, followed by cyclization upon heating with acetic anhydride.

Key Words: CI-911, ^{14}C, ^{3}H, dihydro-1H-pyrrolizine-3,5(2H,6H)-dione, cognition activator

Our program in cognition enhancing agents has previously described the discovery of an attention enhancing agent, CI-844[1], and an anticonfusional agent, pramiracetam[2] (CI-879), which has been labeled.[3] Recently our efforts have turned to the investigation of compounds with broader dose response curves and with activity in behavioral tests suggestive of memory enhancement. These efforts have resulted in the discovery of CI-911, dihydro-1H-pyrrolizine-3,5(2H,6H)-dione[4] (1).

CI-911 was found to have an extraordinarily wide dose response curve in an amnesia reversal test in mice.[5] It improved rodent memory in a test of

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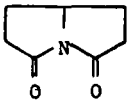

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delayed alternation.[4] It also improved memory in aged monkeys with cognitive impairment.[5]

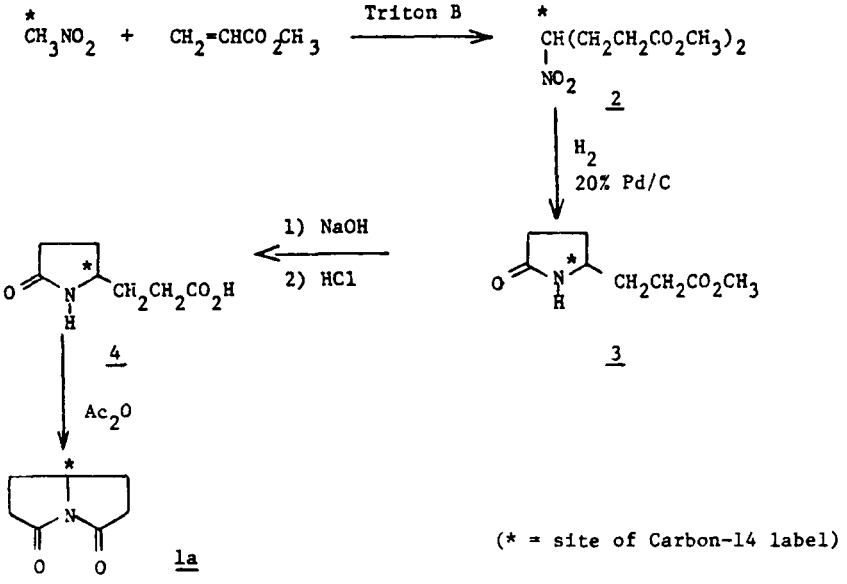
It was necessary to synthesize carbon-14 labeled CI-911 for metabolic and distribution studies, and tritium-labeled compound of high specific activity to study specific receptor binding in the central nervous system.

RESULTS AND DISCUSSION

Carbon-14 Labeling

The synthesis of CI-911 (1) was first described by Lukeš et al.[6] and Leonard et al.[7] in 1947. Subsequent improvements were made by Butler et al.[4] The carbon-14 labeled CI-911 was accomplished in a four-step synthesis using nitromethane-^{14}C as the starting material as shown in Scheme 1. Base-catalyzed Michael addition of nitromethane-^{14}C to methyl acrylate gave the desired di-substituted adduct 2 in addition to the mono- and tri-substituted

Scheme 1

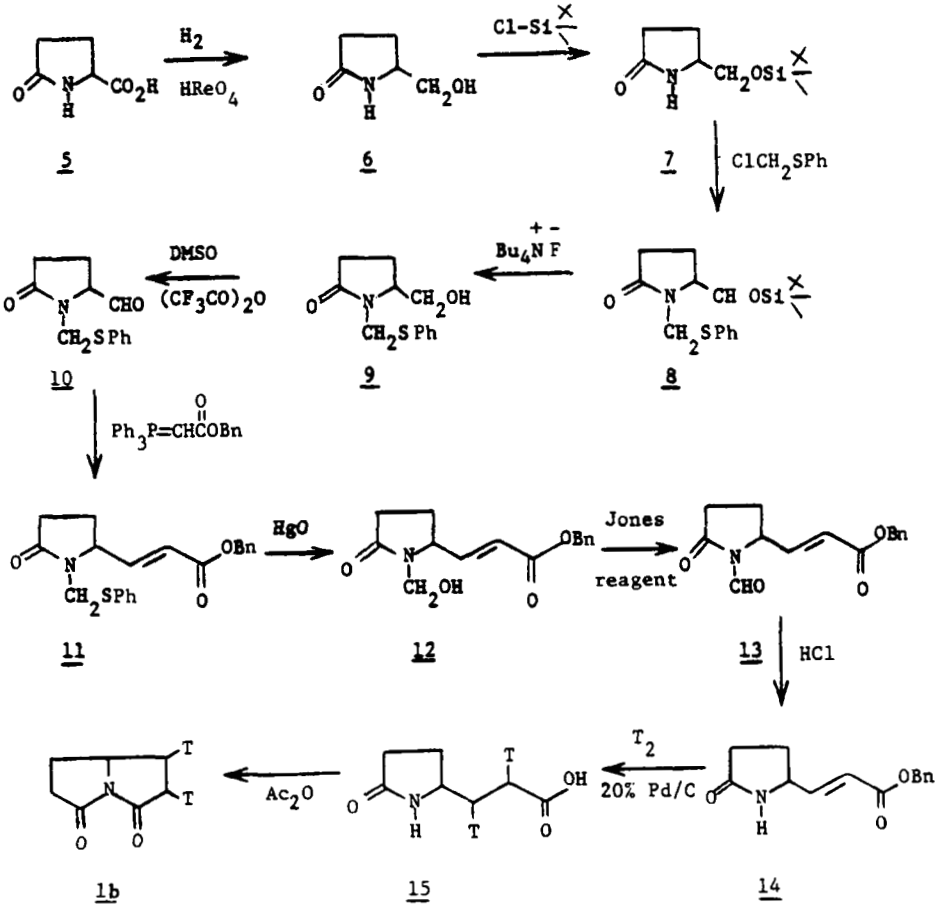


side products.[8] Purification of the mixture by low pressure liquid chromatography gave 2 in 25% radiochemical yield. Hydrogenation of the nitro compound 2 in the presence of 20% palladium on carbon produced 5-oxo-2-pyrrolidine-2-^{14}C-propanoic acid, methyl ester (3). Saponification of 3 yielded the corresponding acid 4. Treatment of 4 with acetic anhydride gave a mixed anhydride intermediate before the final product 1a was produced. The overall radiochemical yield for the carbon-14 synthesis was 9.2%.

Tritium Labeling

Since the standard tritiation exchange condition does not normally produce labeled compound with high enough specific activity for receptor binding studies, a synthetic scheme (Scheme 2) was designed for the specific incorporation of tritium into CI-911.

Scheme 2



5-Oxo-DL-proline (5) was catalytically hydrogenated at 5000 psi in the presence of carbon and perrhenic acid to produce 5-(hydroxymethyl)-2-pyrrolidinone (6) which was protected as a (1,1-dimethylethyl)dimethylsilyl ether 7. Treatment of 7 with NaH followed by [(chloromethyl)thio]benzene gave 5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-[(phenylthio)methyl]-2-pyrrolidinone (8). Desilylation was easily accomplished using tetrabutylammonium fluoride to give a quantitative yield of the alcohol 9. Oxidation of 9 was carried out with DMSO/trifluoroacetic anhydride[9] to yield the corresponding aldehyde 10. Wittig reaction of 10 with phenylmethyl (triphenylphosphoranylidene)acetate gave the α,β-unsaturated ester 11. The phenylthiomethyl protective group was cleaved by treatment with mercuric oxide, oxidation with Jones reagent, and treatment with gaseous HCl to yield 14.

Catalytic reduction of 14 with tritium gas in 2-PrOH/H_2O in the presence of 20% Pd/C produced double-labeled tritiated acid 15 which was subsequently cyclized to the final product 1b upon heating with acetic anhydride. The specific activity of the labeled compound was 28.1 Ci/mmol.

EXPERIMENTAL

^{1}H-NMR spectra were determined on a Varian EM360 (60 mHz), a Bruker WH90 (90 mHz), or a Varian XL-200 (200 mHz) Spectrometer. Chemical shifts were reported in δ (ppm) downfield from tetramethylsilane. Infrared spectra were recorded on a Nicolet XL-1/3600 FT-IR spectrophotometer. Mass spectra were obtained with a Finnigan Series 4000 G.C.-M.S. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Liquid scintillation counting was performed with a Packard 574 liquid scintillation counter using Beckman Ready-Solv MP scintillation cocktail. Microanalyses were performed in house by the Physical and Analytical Section of Warner-Lambert/Parke-Davis.

Thin layer chromatography (TLC) was performed on Analtech or E. Merck silica gel plates (250 μ). Radiochemical purity determinations using TLC plates were performed on a Berthold LB2832 automatic TLC linear analyzer or by

counting sections (5 mm) which were scraped and suspended in MeOH and cocktail before counting. Flash chromatography was carried out on Merck Kieselgel 60 (40-63 nm). Low pressure liquid chromatography (LPLC) was performed using an FMI pump, Merck Lobar Lichroprep Si60 column, and DuPont variable wavelength UV detector at 251 nm. High pressure liquid chromatography (HPLC) was performed using a Spectra Physics SP8700 solvent delivery system, Kratos Spectroflow 773 variable wavelength UV detector, Hewlett-Packard 3390 integrator, and United Technologies Packard Tri-Carb RAM 7500 radioactivity monitor. Gas chromatography (GC) was performed on a Perkin-Elmer model 910 gas chromatograph: Gas Chrom Q (mesh 80-100); OV-17 (6' x 2 mm); 350°C detector; 300°C injector; 100°-300°C column at 10°C/min; silylation with N,N-bis(trimethylsilyl)trifluoroacetamide.

Perrhenic acid was purchased from Shattud Chemical, Denver, Colorado. Nitromethane-^{14}C was purchased from New England Nuclear and was adjusted with carrier to a specific activity of 1.114 mCi/mmol. The catalytic tritium reduction was performed by Midwest Research Institute, Kansas City, Missouri. Authentic unlabeled intermediates and the final product were synthesized in house.

4-Nitroheptanedioic-4-^{14}C acid, dimethyl ester (2).

A solution of nitromethane-^{14}C (40.89 mCi, 1.114 mCi/mmol) in t-BuOH (15 mL) and Triton B (1 mL, 35% in MeOH) was charged slowly with a solution of methyl acrylate (3.31 mL, 36.71 mmol) and t-BuOH (7 mL) below 30°C. The reaction mixture was stirred overnight at room temperature. The unreacted nitromethane-^{14}C was removed in vacuo at room temperature. Distilled water (25 mL) was added to the residue and the resulting deep-orange solution was adjusted to pH 1 with 1 N HCl. The crude product was extracted with methylene chloride (3 x 50 mL). The extract was dried ($MgSO_4$) and the solvent was removed at 60°C in vacuo. The resulting amber oil was purified by LPLC (n-PrOH/n-heptane 3:17; 15 mL/min; retention time (t_r) = 48 min for 2; t_r =

37 min for the mono-substituted nitromethane; 60 min for the trisubstituted nitromethane). The solvent was removed in vacuo to give 10.31 mCi (radiochemical yield 25%) of 2 as an amber oil.

5-Oxo-2-pyrrolidine-2-^{14}C-propanoic acid, methyl ester (3).

4-Nitroheptanedioic-4-^{14}C acid, dimethyl ester (2) (10.31 mCi, 9.25 mmol) in MeOH (100 mL) was hydrogenated in a Parr hydrogenation apparatus for 5.3 h in the presence of 20% Pd/C (220 mg). The reaction mixture was filtered; the filtrate was concentrated in vacuo at 95°C. The resulting viscous yellow oil contained the desired product 3, its free acid 4, and an unidentified component by gas chromatography (ratio 2:3:2) (t_r of 3 = 11.6 min; t_r of 4 = 12.4 min; t_r of 2 = 12.6 min). The crude material was used for conversion to the corresponding acid without purification.

5-Oxo-2-pyrrolidine-2-^{14}C-propanoic acid (4).

The crude ester 3 in MeOH (10 mL) was filtered and 1 N NaOH (10.64 mL) was added. The solution was refluxed with stirring for 24 h. TLC analysis (CH_2Cl_2/Acetone/MeOH/NH_4OH 70:20:10:1, Analtech silica gel) showed the radiochemical purity to be 97% as the acid 4 with no precursor remaining. The solvent was removed in vacuo at room temperature to half of the original volume. After the pH was adjusted from 10 to 1 with HCl, the remaining solvent was removed in vacuo at 65°C. The residue was used in the next reaction without purification.

Dihydro-1H-pyrrolizine-3,5(2H,6H)dione-7a-^{14}C, CI-911-^{14}C (1a).

A mixture of the acid 4 and acetic anhydride (30 mL) was stirred at 95°C for 4 h. TLC analysis (CH_2Cl_2/Acetone/MeOH/NH_4OH 70:20:10:1, Analtech silica gel) showed the radiochemical purity to be 73% as 1a, 17% as unreacted 4 and the remainder as several unidentified components. The crude reaction mixture was filtered to remove insoluble material. The solvent was removed in vacuo at 60°C. The resulting residue was sublimed for three days to give

1a as a yellow-white solid (1.07 g, 83% chemical yield from 2).

Recrystallization from toluene resulted in a light tan solid (0.8 g). Its radiochemical purity by TLC (same system as described above) was 89%. Purification on a silica gel column eluted with methylene chloride/acetone 1:1 gave 1a (3.777 mCi, 511 mg, 1.028 mCi/mmol) as a white solid: radiochemical purity $\geq$ 99.2% by TLC analysis in three systems (Analtech silica gel a. CH_2Cl_2/Acetone 1:1, R_f = 0.55; b. CH_2Cl_2/Acetone/MeOH/NH_4OH 70:20:10:1, R_f = 0.62; c. CH_2Cl_2/EtOAc/MeOH 2:2:1, R_f = 0.63); chemical purity = 99% by GC (t_r = 15 min); mp 180°-182°C, identical to that of a reference sample; ^1H-NMR (90 mHz, $CDCl_3$) δ 1.5-3.0 (m, 8H), 4.1-4.6 (m, 1H).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.16; H, 6.52; N, 9.95.

5-(Hydroxymethyl)-2-pyrrolidinone (6).

A mixture of 5-oxo-DL-proline (5) (200 g, 1.55 mol), carbon (Darco G-60, 20 g), perrhenic acid (4 mL, 1.5 g Re/mL H_2O), and water (800 mL) were placed in an autoclave. The reduction was carried out at 5,000 psi constant pressure and 200°C. Hydrogen uptake was monitored using a calibrated reservoir. The reduction was completed in 10 h, and the mixture was cooled and filtered through Celite. After removal of water by evaporation in vacuo a black viscous oil was obtained. This material was distilled (185°C/0.4 torr) to afford 114.6 g (64%) of white solid 6: mp 64-66°C; ^1H-NMR (90 mHz, $CDCl_3$) δ 7.30 (s, 1H broad), 4.33 (s, 1H), 3.3-3.9 (m, 3H), 1.5-2.5 (m, 4H); IR (film) 2960, 1750, 1695, 1442, 1220 cm^{-1}.

Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.18; H, 7.60; N, 12.08.

5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-pyrrolidinone (7).

To a mixture of DMF (40 mL) and 5-(hydroxymethyl)-2-pyrrolidinone (6) (20 g, 0.174 mol) was added imidazole (17.6 g, 0.29 mol) and (1,1-dimethylethyl)dimethylsilyl chloride (34 g, 0.23 mol). The reaction mixture was stirred overnight and diluted with ethyl acetate (400 mL). The

precipitated imidazole was removed by filtration and the volatiles were removed in vacuo. The residue was passed through a small amount of silica gel using ethyl acetate as eluant to remove any remaining imidazole. Evaporation of the ethyl acetate gave 32.1 g (81%) of the silyl ether 7: mp 40-42°C; ^{1}H-NMR (60 mHz, $CDCl_3$) δ 7.10 (s, 1H broad), 3.5-3.9 (m, 3H), 1.7-2.5 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H); IR (film) 3175, 2930, 2840, 1695, 1450, 1250, 1110, 835, 770 cm^{-1}.

5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1-[(phenylthio)methyl]-2-pyrrolidinone (8).

To a magnetically stirred mixture of 50% NaH oil dispersion (9.0 g, 0.19 mol) and toluene (300 mL) was added 5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-2-pyrrolidinone (7) (41.6 g, 0.18 mol). The mixture was stirred for 48 h and [(chloromethyl)thio]benzene (32.0 g, 0.20 mol) was added at room temperature. The mixture was warmed to 80°C for 4 h and stirred overnight at room temperature. The mixture was filtered through Celite and evaporated in vacuo. The crude material was purified by flash chromatography on 600 g of silica gel using methylene chloride to remove the unreacted sulfide followed by elution with ethyl acetate to obtain 50.3 g (79%) of a clear oil 8: ^{1}H-NMR (60 mHz, $CDCl_3$) δ 7.2-7.7 (m, 5H), 7.51 (d, 1H, J = 13 Hz), 4.30 (d, 1H, J = 13 Hz), 3.5-4.3 (m, 3H), 1.8-2.6 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H); IR (film) 2925, 2830, 1690, 1405, 1240, 1105, 835, 770, 735 cm^{-1}.

5-(Hydroxymethyl)-1-[(phenylthio)methyl]-2-pyrrolidinone (9).

To 5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-[(phenylthio)-methyl]-2-pyrrolidinone (8) (50.3 g, 0.14 mol) was added tetrabutylammonium fluoride in THF (1.0 M, 110 mL). The solution was stirred for 1 h, and diluted with water (200 mL) and ethyl acetate (400 mL). The organic phase was washed with brine, dried ($MgSO_4$), filtered, and the solvent was removed in vacuo to give 34.4 g (100%) of the alcohol 9 which crystallized upon standing: mp 51-53°C; ^{1}H-NMR (60 mHz, $CDCl_3$) δ 7.1-7.6 (m, 5H), 5.20 (d, 1H, J = 14 Hz), 3.3-4.2 (m, 3H), 3.2 (s, 1H broad), 1.7-2-6 (m, 4H); IR (film)

3325, 2950, 1685, 1670, 1435, 1240, 740, 685 cm^{-1}.

3-[5-Oxo-1-[(phenylthio)methyl]-2-pyrrolidinyl]-2-propenoic acid, phenylmethyl ester (11).

To a magnetically stirred solution of DMSO (1.95 mL) in dry methylene chloride (12 mL) at -50°C under N_2 atmosphere was added trifluoroacetic anhydride[9] (3.0 mL) and methylene chloride (7 mL) over a 10 min period. The solution was stirred at -50°C for 10 min and the alcohol 9 (3.3 g, 0.0139 mol) was added in methylene chloride (8 mL). The mixture was stirred at -50°C for 40 min and diisopropylethylamine (6.0 mL) was added. The solution was warmed to room temperature and diluted with water (100 mL) and methylene chloride (50 mL). The organic layer was washed with brine (2X), dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude aldehyde 10.

The crude 10 was dissolved in methylene chloride (25 mL) and phenylmethyl (triphenylphosphoranylidene)acetate (6.2 g, 0.015 mol) was added. The mixture was stirred for 1 h and the solvent was removed in vacuo. Chromatography on silica gel with ethyl acetate afforded 3.7 g (72%) of 11: ^{1}H-NMR (60 mHz, $CDCl_3$) δ 7.1-7.6 (m, 10H), 6.70 (dd, 1H, J = 15 Hz, 8 Hz), 5.74 (d, 1H, J = 15 Hz), 5.33 (d, 1H, J = 14 Hz), 5.18 (s, 2H), 4.2-4.5 (m, 1H), 4.02 (d, 1H, J = 14 Hz), 1.8-2.4 (m, 4H); IR (film) 3060, 2950, 1243, 1182, 745, 695 cm^{-1}.

Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81. Found: C, 68.91; H, 5.78; N, 3.76.

3-(1-Formyl-5-oxo-2-pyrrolidinyl)-2-propenoic acid, phenylmethyl ester (13).

To a magnetically stirred solution of water (38 mL), THF (212 mL), and BF_3 etherate (11.1 mL) was added red mercuric oxide (9.74 g, 45 mmol). After stirring for 5 min a solution of 3-[5-oxo-1-[(phenylthio)methyl]-2-pyrrolidinyl]-2-propenoic acid, phenylmethyl ester (11) (16.8 g, 45 mmol) in THF (20 mL) was added over a 5 min period. The reaction mixture was stirred for 1 h, diluted with brine (300 mL) and extracted with Et_2O (400 mL). The organic layer was washed (2X) with brine, dried ($MgSO_4$), filtered and

evaporated in vacuo.

The crude N-hydroxymethyl compound 12 obtained was stirred in acetone (100 mL) and treated with Jones reagent until the red color persisted for 15 min. The crude mixture was treated with methanol (25 mL), stirred for an additional 10 min and diluted with brine (200 mL) and Et_2O (200 mL). The organic layer was washed (2X) with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Chromatography on silica gel with ethyl acetate as eluant afforded 6.37 g (51%) of 13: ^{1}H-NMR (90 mHz, $CDCl_3$) δ 9.01 (s, 1H), 7.30 (s, 5H), 6.72 (dd, 1H, J = 14 Hz, 6 Hz), 5.86 (dd, 1H, J = 14 Hz, 2.0 Hz), 5.12 (s, 2H), 4.81 (t, 1H, J = 7 Hz), 1.7-2.7 (m, 4H); IR (film) 2880, 1752, 1700, 1275, 1182, 700 cm^{-1}.

3-(5-Oxo-2-pyrrolidinyl)-2-propenoic acid, phenylmethyl ester (14).

A solution of 3-(1-formyl-5-oxo-2-pyrrolidinyl)-2-propenoic acid, phenylmethyl ester (13) (6.37 g, 23.3 mmol) and benzyl alcohol (125 mL) was treated with gaseous HCl for 5 min and stirred at room temperature for 2 h. The excess benzyl alcohol was removed by distillation at water aspirator pressure. The resulting residue was chromatographed on silica gel with EtOAc as eluant to afford 4.92 g (86%) of 14: ^{1}H-NMR (90 mHz, $CDCl_3$) δ 7.31 (s, 1H), 6.88 (dd, 1H, J = 15 Hz, 5.5 Hz), 6.7-6.9 (s, 1H broad), 5.93 (dd, 1H, J = 15 Hz, 2 Hz), 5.08 (s, 2H), 4.27 (q, 1H, J = 6 Hz), 1.6-2.5 (m, 4H); IR (film) 3220, 1700, 1660, 1270, 1175, 985, 755, 700 cm^{-1}; mass spectrum m/e 246 (M^+ +1), 154 (M^+ -C_7H_7), 91 (B, C_7H_7).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.36; H, 5.88; N, 5.73.

5-Oxo-2-pyrrolidinepropanoic-α,β-$^3H_2$ acid (15).

A mixture of 14 (3.7 mg), 20% palladium on carbon, 2-propanol (0.5 mL) and water (1.0 mL) was stirred overnight under a T_2 (10 Ci) atmosphere. The mixture was filtered through a bed of Celite to remove the catalyst and the catalyst was washed with 2-propanol. The solution was concentrated in vacuo. The residue was dissolved in 10% THF in H_2O and the solvent was distilled off in vacuo. The distillation was repeated twice with 10% THF in H_2O. A total

of 406 mCi of the crude 15 was recovered (92% radiochemical purity by TLC: a. $CHCl_3$/EtOH/NH_4OH 10:30:1, R_f = 0.25; b. EtOAc/MeOH/HCOOH 1:1:0.01, R_f = 0.48).

Dihydro-1H-pyrrolizine-3,5(2H,6H)-dione-1,2-$^{3}H_2$ (1b).

A solution of crude 5-oxo-2-pyrrolidinepropanoic-α,β-$^{3}H_2$ acid (15) (406 mCi) and acetic anhydride (1.0 mL) was heated at 60°C for 27 h. The solution was cooled to room temperature overnight. The acetic anhydride was evaporated in vacuo at 50°C. The crude product was purified by TLC (E. Merck) which was developed twice with methylene chloride/diethyl ether 1:1. The band corresponding to the product was scraped and eluted with methylene chloride/acetone 1:1. A total of 264 mCi of 1b (91% radiochemical purity) was recovered. A 13.2 mCi aliquot of the product was further purified by the same TLC system as described above. 7.7 mCi of 1b was recovered at > 99% radiochemical purity by TLC (a. CH_2Cl_2/Et_2O 1:1, R_f = 0.07; b. CH_2Cl_2/acetone 1:1. R_f = 0.37; c. CH_2Cl_2/EtOAc/MeOH 2:2:1, R_f = 0.47).

The specific activity of 1b was determined using HPLC and liquid scintillation counting. A sample of 1b was diluted with water and 1-methyl-2-pyrrolidinone was added as an internal standard. The sample was analyzed by HPLC: t_r of 1b = 6.35 min, t_r of 1-methyl-2-pyrrolidinone = 5.55 min (Alltech Lichrosorb RP-2, 4.6 mm I.D. x 25 cm, 10 μ; 3% 2-propanol in water; UV @ 220 nm; flow rate 1.5 mL/min). The specific activity was determined to be 28.1 Ci/mmol.

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