SYNTHESIS OF 5-ETHYL-1,3,8-TRIMETHYL-1H-[5-^{14}C] IMIDAZO[1,2-c]PYRAZOLO[3,4-e]PYRIMIDINE

J. L. Hicks and C. C. Huang

Chemistry Department, Warner-Lambert/Parke-Davis Pharmaceutical Research
2800 Plymouth Road, Ann Arbor, Michigan 48105

SUMMARY

5-Ethyl-1,3,8-trimethyl-1H-imidazo[1,2-c]pyrazolo[3,4-e]pyrimidine, a new antipsychotic agent, was labeled with ^{14}C. The labeled compound was synthesized from barium [^{14}C]carbonate in four steps. [1-^{14}C]Propanoic acid, made from $^{14}CO_2$ and ethylmagnesium bromide, was treated with 5-(4,5-dihydro-4-methyl-1H-imidazol-2-yl)-1,3-dimethyl-4-nitro-1H-pyrazole in the presence of dicyclohexylcarbodiimide to give 2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)-4,5-dihydro-4-methyl-1-(1-[1-^{14}C]oxopropyl)-1H-imidazole. This was reduced and cyclized to 5-ethyl-7,8-dihydro-1,3,8-trimethyl-1H-[5-^{14}C]imidazo[1,2-c]pyrazolo[3,4-e]pyrimidine. Oxidation gave the title compound in an overall radiochemical yield of 35% with a specific activity of 4.88 mCi/mmol.

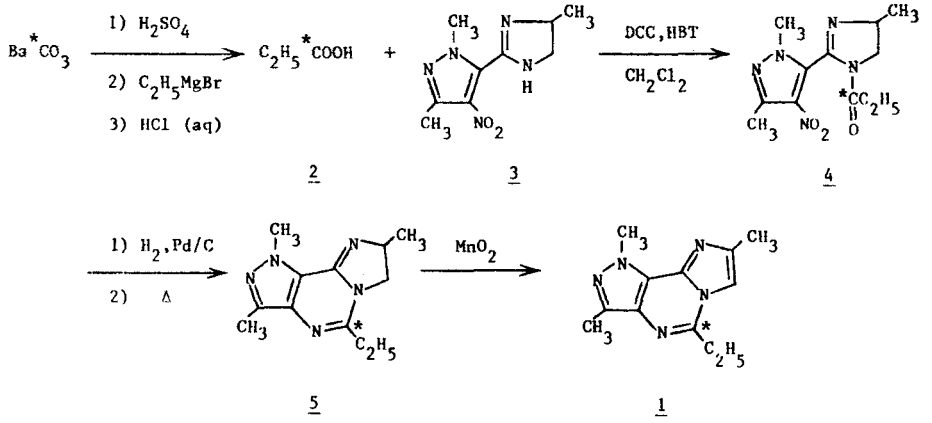
Keywords: 5-Ethyl-1,3,8-trimethyl-1H-[5-^{14}C]imidazo[1,2-c]pyrazolo[3,4-e]-pyrimidine, ^{14}C, antipsychotic

INTRODUCTION

5-Ethyl-1,3,8-trimethyl-1H-imidazo[1,2-c]pyrazolo[3,4-e]pyrimidine (PD 112,488) (1) is a newly discovered agent for the treatment of psychosis. This compound shows antipsychotic activity as demonstrated in the mouse activity,[1] screen test,[2] and the conditioned avoidance-escape procedure.[3] The synthesis of the ^{14}C labeled 1 was necessary to study its metabolism and bioavailability. The synthesis of a number of alkylimidazo[1,2-c]pyrazolo-[3,4-e]pyrimidines including 1 was reported by DeWald.[4,5] Our synthesis of ^{14}C labeled 1 from [1-^{14}C]propanoic acid, which was made from barium [^{14}C]carbonate (Scheme), was based on modifications of the procedures by DeWald.

0362-4803/85/090947-06$01.00

Received April 2, 1985



Scheme (* denotes location of ^{14}C)

RESULTS AND DISCUSSION

[1-^{14}C]Propanoic acid (2) was synthesized by a Grignard reaction between ethylmagnesium bromide and $^{14}CO_2$, liberated from barium [^{14}C]-carbonate.[6] The radiochemical yield was 96%.

The coupling of 2 with 5-(4,5-dihydro-4-methyl-1H-imidazol-2-yl)-1,3-dimethyl-4-nitro-1H-pyrazole (3) in the presence of dicyclohexylcarbodiimide (DCC) and 1H-benzotriazol-1-ol produced 2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)-4,5-dihydro-4-methyl-1-(1-[1-^{14}C]oxopropyl)-1H-imidazole (4) in an 87% radiochemical yield.[7] This was a deviation from the original procedure of DeWald[4,5] who treated 3 with propanoic anhydride. We chose not to use ^{14}C labeled propanoic anhydride because of the extra steps involved in making it and the potential loss of one half of the label.

The nitro compound 4 was reduced to an amine by hydrogenation with palladium on carbon as the catalyst in propanoic acid. A portion of the amine cyclized to give 5-ethyl-7,8-dihydro-1,3,8-trimethyl-1H-[5-^{14}C]imidazo[1,2-c]pyrazolo[3,4-e]pyrimidine (5) during the hydrogenation and subsequent removal of the propanoic acid. The cyclization was completed by heating the mixture in refluxing xylene. After chromatography, 5 was recovered in a 53% radiochemical yield.

We attempted the oxidation of 5 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ) in toluene. The disappearance of 5 and formation of 1 was rapid as determined by thin layer chromatography(TLC). Upon workup, however, it was found that >90% of the mass was associated with a polar material, possibly a complex formed with the DDQ.[8] Similar results were reported by Bhat and Townsend[9] that they were unable to oxidize 2,3-dihydro-7-β-D-ribofuranosylimidazo[1,2-c]pyrazolo[4,3-e]pyrimidine, a compound analogous to 5, to the fully aromatic system with DDQ or manganese(IV) oxide in methylene chloride. However, DeWald[4,5] was able to effect the oxidation of 7,8-dihydroimidazo[1,2-c]pyrazolo[3,4-e]pyrimidines with activated manganese(IV) oxide in toluene. Thus 5 was converted to 1 using a large excess of activated manganese(IV) oxide in toluene in a 59% radiochemical yield after recrystallization. The chemical and radiochemical purity of the final product was >99%.

EXPERIMENTAL

^{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 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-Solve MP liquid scintillation cocktail.

EM Merck silica gel plates (250 μ) were used for thin layer chromatography (TLC). 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, Hewlett-Packard 3390A integrator and United Technologies Packard Tri-Carb RAM 7500 radioactivity monitor.

Barium [^{14}C]carbonate was purchased from Research Products International Corp., Mount Prospect, Illinois. Ethylmagnesium bromide was obtained from Aldrich Chemical Co. Activated manganese(IV) oxide was purchased from

General Metallic Oxides. 5-(4,5-Dihydro-4-methyl-1H-imidazol-2-yl)-1,3-dimethyl-4-nitro-1H-pyrazole was supplied by Chemical Development, Warner-Lambert/Parke-Davis Pharmaceutical Research, Holland, Michigan.

[1-^{14}C]Propanoic acid (2). Barium [^{14}C]carbonate (39.6 mCi, 6.604 mmol, specific activity 6.0 mCi/mmol) was treated with concentrated sulfuric acid (30 mL). The liberated $^{14}CO_2$ was passed through a column of anhydrous calcium sulfate and transferred to a flask containing ethylmagnesium bromide (7.0 mmol) in diethyl ether (10 mL) by standard vacuum line techniques. The flask was warmed to room temperature and stirred for 2.5 h. Any excess $^{14}CO_2$ was removed by cooling the reaction flask to -78°C (dry ice/acetone) and applying a vacuum. The reaction mixture was warmed to room temperature and treated with 6 M HCl (2.0 mL). Anhydrous magnesium sulfate (2.5 g) was added to the clear two-phase mixture to remove the water. The diethyl ether solution was filtered, further dried ($MgSO_4$), filtered, and evaporated in vacuo to give 38.0 mCi (96% radiochemical yield) of 2 as a colorless liquid. The product was used without characterization in the next step.

2-(1,3-Dimethyl-4-nitro-1H-pyrazol-5-yl)-4,5-dihydro-4-methyl-1-(1-[1-^{14}C]oxopropyl)-1H-imidazole (4). A solution of 1H-benzotriazol-1-ol hydrate (852 mg, 6.31 mmol) in CH_2Cl_2 (40 mL) was added to [1-^{14}C]-propanoic acid (38 mCi, 6.31 mmol) forming a white precipitate. 3 (1.409 g, 6.31 mmol) was added and a yellow solution formed. The solution was cooled to 0°C and a precipitate formed. Dicyclohexylcarbodiimide (1.30 g, 6.31 mmol) in CH_2Cl_2 (20 mL) was added slowly to the slurry. The reaction mixture was warmed to room temperature and stirred for 4.5 h. The mixture was filtered and the solvent was evaporated in vacuo to give 33.2 mCi (87% radiochemical yield) of 4: TLC, Rf = 0.31, radiochemical purity >98%, EtOAc:EtOH:Et_3N (75:25:1), cochromatographed with authentic unlabeled 4.

5-Ethyl-7,8-dihydro-1,3,8-trimethyl-1H-[5-^{14}C]imidazo[1,2-c]pyrazolo-[3,4-e]pyrimidine (5). A mixture of the crude 4, propanoic acid (30 mL), and 10% palladium on carbon (10 mg) was hydrogenated at 45 psi using a Parr

hydrogenation apparatus for 17 h. The mixture was filtered through Celite and the solvent evaporated in vacuo at 50°C. The residual acid was removed by codistillation with xylene (2 x 50 mL). The residue was refluxed in xylene for 4 h and the solvent was removed in vacuo. The material was chromatographed on silica gel (2 x 55 cm) eluting with EtOAc:EtOH:Et_3N (75:25:1) to give 20.2 mCi (53% radiochemical yield) of 5: TLC, Rf = 0.17, radiochemical purity >97%, EtOAc:EtOH:Et_3N (75:25:1), cochromatographed with authentic unlabeled 5.

5-Ethyl-1,3,8-trimethyl-1H-[5-^{14}C]imidazo[1,2-c]pyrazolo[3,4-e]-pyrimidine (1). Manganese(IV) oxide (3.0 g) was dried by azeotropic distillation with toluene for 3 h. To the mixture was added 5 (20.2 mCi) in toluene to a total volume of 50 mL and refluxed for 16 h. The mixture was filtered through Celite and the toluene was evaporated in vacuo. The solid was returned to an additional 3.0 g of manganese(IV) oxide (dried as before) in 50 mL of toluene and refluxed for 2.5 h. The mixture was filtered through Celite and evaporated in vacuo to yield 19.2 mCi of a yellow solid. The material was recrystallized from EtOAc to give 651 mg (13.9 mCi, 2.84 mmol, 69% radiochemical yield) of 1: m.p. 182.0° - 182.5°C; specific activity 4.88 mCi/mmol; TLC, radiochemical purity >99%, R_f = 0.51, EtOAc:EtOH:Et_3N (75:25:1); R_f = 0.12, $PhCH_3$:Et_3N (19:1), R_f = 0.59, MeOH; HPLC, retention time 6.0 min, radiochemical purity >99%, Alltech Silica 600, 10 μ, 4.6 mm ID x 25 cm; CH_2Cl_2:MeOH:conc. NH_4OH (98.5:1.5:0.15); flow rate 1.0 mL/min; uv @ 248 nm; ^{1}H-NMR(90 MHz, $CDCl_3$) 7.32(d, 1H, J=1 Hz), 4.35(s, 3H), 3.04(q, 2H, J=7 Hz), 2.57(s, 3H), 2.48(d, 3H, J=1 Hz), 1.48(t, 3H, J=7 Hz); IR(KBr) 3117, 2975, 2935, 1659, 1568, 1508, 1382, 1310, 1217, 903, 743, 694, 629 cm^{-1}; Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.86; H, 6.60; N, 30.54. Found: C, 62.88; H, 6.39; N, 30.74.

ACKNOWLEDGMENT

The authors thank Dr. H. A. DeWald for helpful discussions concerning this project, Dr. J. R. Zellar, Chemical Development, Warner-Lambert/Parke-

Davis, Holland, MI, for providing 5-(4,5-dihydro-4-methyl-1H-imidazol-2-yl)-1,3-dimethyl-4-nitro-1H-pyrazole, and the Analytical and Physical Chemistry Section, Warner-Lambert/Parke-Davis for obtaining analytical and spectral data.

REFERENCES

1. Parker, R. B.-Life Sciences 22,1067(1978).

2. Coughenour, L. L., McLean, J. R., and Parker, R. B.-Pharm. Biochem. Behav. 6,351(1977).

3. A modification of the procedure of Cook, L. and Weidley, E.-Ann. NY Acad. Sci. 740(1957).

4. DeWald, H. A., US Patent 4,469,868, Warner-Lambert Co., 1984.

5. DeWald, H. A., Beeson, N., Wise, L. D., Downs, D., and Heffner, T. Submitted for publication in J. Med. Chem. 1985.

6. Murry, A. and Williams, D. L.-Organic Synthesis with Isotopes, Interscience Publishers Inc., New York, 1958, p. 86.

7. a) Sheehan, J. C. and Hess, G. P.-J. Am. Chem. Soc. 77,1067(1955).
   b) Bonner, W. A. and McNamel, P. I.-J. Org. Chem. 26,2554(1961).

8. Walker, D. and Hiebert, J. D.-Chem. Rev. 67,153(1967).

9. Bhat, G. A. and Townsend, L. B.-J. Chem. Soc. Perkin I,2387(1981).