SYNTHESIS OF 5-HYDROXY-[6-^{14}C]-METHYL-2-di-n-PROPYLAMINOTETRALIN

Dale L. Koble and Lawrence J. Fischer

Department of Pharmacology, College of Medicine
The University of Iowa, Iowa City, Iowa 52242

SUMMARY

By an improved synthesis, 5-hydroxy-6-methyl-2-di-n-propylaminotetralin (DK-118), a dopamine agonist, has been obtained in only six steps and in greater than 10% overall yield. This new synthesis has been used for the preparation of 5-hydroxy-[6-^{14}C]-methyl-2-di-n-propylaminotetralin (I) to be used in metabolic studies. The ^{14}C-radiolabel was introduced near the end of the synthesis by an ortho-specific formylation procedure using ^{14}C-paraformaldehyde.

Key Words: Dopamine agonist, DK-118, Carbon-14

INTRODUCTION

The dopamine receptor stimulating properties of 5-hydroxy-6-methyl-2-di-n-propylaminotetralin (DK-118) (I) have been previously reported.[1,2] Recent evidence indicates that some of the dopaminergic effects of this compound may be due to the production of an active metabolite.[3] This is not unexpected since SAR studies of the 2-aminotetralin nucleus have demonstrated that a variety of substitution and variation[4,5] is consistent with dopaminergic activity. It is possible, therefore, that biotransformation of these drugs may result in the formation of active as well as inactive metabolites.

0362-4803/84/060519-06$01.00

Received June 20, 1983
Revised February 9, 1984

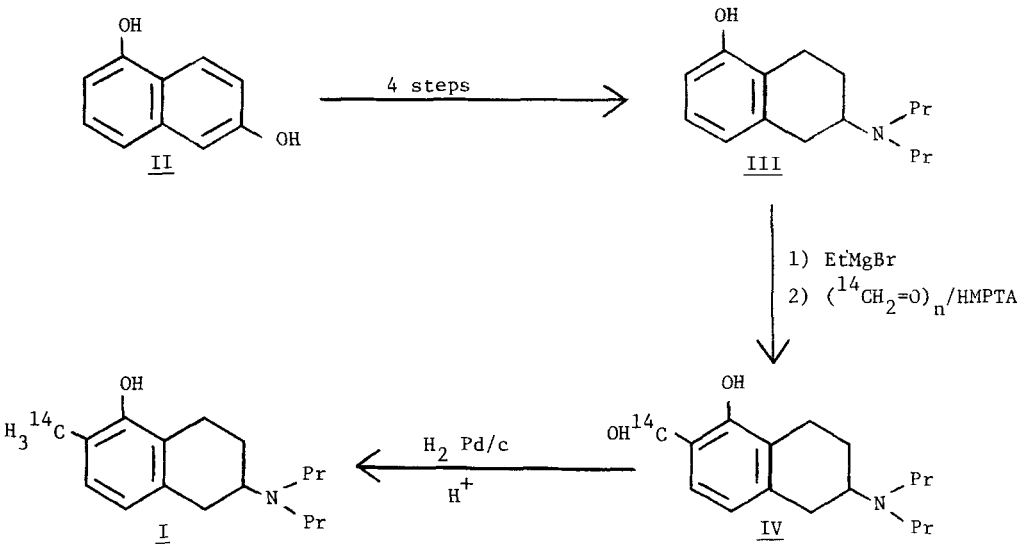
In order to investigate the metabolic fate of DK-118, it was desired to synthesize labelled compound with carbon-14 in a metabolically stable position. Since the original synthesis[1] of DK-118 was prohibitively long for this use, a shorter synthetic procedure in which a carbon-14 label could be conveniently introduced was required.

RESULTS AND DISCUSSION

5-Hydroxy-2-di-n-propylaminotetralin (III) is readily available[6] via a short literature synthesis beginning with commercially available 1,6-dihydroxynaphthalene (II). Functionalization of (III) at the 6 position with a carboxyl, formyl or hydroxymethylene group would then give a derivative which could be easily converted to DK-118. Previous attempts at the ortho-specific functionalization of (III) or a derivative thereof by a variety of methods were unsuccessful.[7] Casnati et al.[8] originally reported the selective ortho-formylation of magnesium phenoxides. Casiraghi et al.[9] (also see ref. 10) have obtained significantly improved yields in a modification of this procedure. This modification consists of the reaction of hexamethylphosphoramide (HMPTA) complexes of magnesium phenoxides with paraformaldehyde. The addition of HMPTA inhibits the formation of undesired quinone-methide intermediates which lead to polymerization. This method proved to be highly successful for the conversion of (III) to (IV).

The specific activity of the product DK-118 was less than half that of the ^{14}C-paraformaldehyde-carrier mixture. This can be accounted for by the larger particle size of the ^{14}C-paraformaldehyde used in the reaction as compared to the carrier paraformaldehyde and the effect of this difference on their relative rates of depolymerization. No attempt was made to circumvent this difficulty, and it is emphasized that a much higher radiochemical yield could be obtained by performing the reaction without the addition of carrier paraformaldehyde.

5-Hydroxy-6-methyl-2-di-n-propylaminotetralin (IV) was reduced catalytically over palladium on carbon under acidic conditions to give the title compound (I) in 51% chemical yield and 8% radiochemical yield from (III).



SCHEME I

Since it is refractory to oxidative loss, the benzylic position is a desirable one for the ^{14}C-labeling of many organic compounds for metabolism experiments. The present work demonstrates the utility of a regiospecific ortho-formylation procedure for this purpose. The characteristics of this reaction (high yield, mild reaction conditions and high regiospecificity), combined with the usefulness of the aldehyde functionality in organic synthesis, should make this procedure a method of choice for the synthesis of a variety of benzylic C-14-labeled compounds.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian Associates EM-360A spectrometer using Me_4Si as the internal standard. Melting points are uncorrected. Radioactivity was determined with a Packard Tricarb scintillation spectrometer model 3320.

5-Hydroxy-6-methyl-2-di-n-propylaminotetralin (DK-118) Hydrobromide

This was prepared essentially the same as the radiolabeled material except that the HBr salt was prepared for melting-point comparison with authentic DK-118. m.p. 186°C Lit (1) 180-184°C; m.s. m/e 261 (M^+-HBr); n.m.r. (CD_3OD) δ 1.04 (t, 6H), 1.51 - 2.14 (m, 4H), 2.17 (s, 3H), 6.56 (d, 1H), 6.86 (d, 1H). The free base was co-chromatographed with authentic DK-118 free base and showed identical behavior; Et_2O/CH_2Cl_2 8:2 rf = 0.40, ØH/MeOH 4.5:1 rf = 0.55.

5-Hydroxy-[6-^{14}C]-formyl-2-di-n-propylaminotetralin (IV)

To an oven-dried flask under N_2 equipped with a magnetic stirring bar was added 0.3 mL (0.0008 moles) of 2.8 M EtMgBr in Et_2O (Aldrich). Most of the Et_2O was flushed off with dry N_2, 10 mL of dry benzene added, and this solution heated at 80°C for a few minutes to remove any remaining Et_2O. After cooling to room temperature, 2-di-n-propylamino-5-hydroxytetralin (III) (207 mg, 0.837 mmol) in 20 mL of dry benzene was added dropwise. After 5 minutes stirring, 0.2 mL of hexamethylphosphortriamide (HMPTA) (0.001 moles) was added and the solution stirred for 0.5 hr. A mixture of 1.7 mg of ^{14}C-paraformaldehyde (1 mCi, NEN) and 61 mg of paraformaldehyde was added and any large crystals of paraformaldehyde crushed with a glass stirring rod. The mixture was refluxed at 80°C for 4 hr, cooled, and stirred with 20 ml of 5% HCl for 15 min. The aqueous layer was separated and the organic phase extracted 3 x 25 ml with dilute HCl. The combined acidic solutions were brought to pH 8 with $NaHCO_3$ and extracted with $CHCl_3$ 4 x 75 mL. The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, evaporated and chromatographed on a silica gel column eluting with 2% EtOH/benzene. The collected aldehyde gave one spot on silica gel (benzene/MeOH, 4.5:1) Rf = 0.54 and, after evaporation of solvent, was used in the next reaction.

5-Hydroxy-6-methyl-2-di-n-propylaminotetralin (I) Hydrochloride

The aldehyde from the above reaction was dissolved in 100 mL of absolute EtOH with 200 mg of 5% Pd/C and this solution brought to pH 2 (pH paper) with conc. HCl. The solution was shaken on a Parr hydrogenation apparatus for 72 hr at an initial pressure of 30 psig. THe reduction mixture was filtered (celite), the catalyst on the filter washed with hot EtOH and the combined ethanolic solutions evaporated. The residue was dissolved in 50 ml H_2O, this solution brought to pH 10 with Na_2CO_3 and then extracted several times with equal volumes of $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4), evaporated and the residue purified by preparative scale tlc (Analtech Uniplate-T Taper Plates, S.G.G.F.) using benzene/ethanol (8:2) as the mobile phase. The area on the plate corresponding to product was collected, a few drops of H_2O added to the silica gel and the product eluted with acetone. The combined acetone extracts were evaporated and the small amount of H_2O in the residue removed as an azeotrope by repeated evaporation of benzene. A small amount of HCl gas was added to a benzene solution of the dry product and the benzene evaporated. Dry benzene was added several times to the residue and evaporated to bring the solution to neutrality and evaporation of the last benzene solution gave a white crystalline product. Chemical yield: 124.7 mg (51% from III) Radiochemical yield: 0.08 mCi (8%), specific activity 0.19 mCi/mmole, radiochemical purity > 97%. m.s. m/e 261 (M^+ - HCl).

ACKNOWLEDGMENTS

Support for this research was provided by United States Public Health Service Grant GM22365. We are indebted to Dr. J.G. Cannon for the provision of laboratory facilities for a portion of this work.

REFERENCES

1. Cannon, J.G., Koble, D.L., Long, J.P. and Verimer, T. - J. Med. Chem. 23: 750 (1980).

2. Verimer, T., Long, J.P., Bhatnagar, R.K., Koble, D.L., Cannon, J.G., Flynn, J.R., Goodale, D.B. and Arnerić, S.P. - Arch. Int. Pharmacodyn. Ther. 250: 221 (1981).

3. Cannon, J.G., Furlano, D.C., Koble, D.L., Koons, J.C. and Long, J.P. - Life Sci. (in press).

4. Cannon, J.G., Lee, T., Goldman, H.D., Costall, B. and Naylor, R.J. - J. Med. Chem. 20: 1111 (1977).

5. Cannon, J.G., Brubaker, A.N., Long, J.P., Flynn, J.R., Verimer, T., Harnirattisai, P., Costall, B., Naylor, R.J. and Nohria, V. - J. Med. Chem. 24: 149 (1981).

6. Hacksell, U., Svensson, V., Nilsson, J.L.G., Hjorth, S., Carlsson, A., Wikstrom, H., Lindberg, P. and Sanchez, D. - J. Med. Chem. 22: 1469 (1979).

7. Koble, D.L. - Thesis, University of Iowa, U.S.A. (1980).

8. Casnati, G., Crisafulli, M. and Ricca, A. - Tetrahedron Lett. 243: (1965).

9. Casiraghi, G., Casnati, G., Cornia, M., Pochini, A., Puglia, G., Sartori, G. and Ungaro, R. - J. Chem. Soc. Perkin I 318 (1978).

10. Casiraghi, G., Casnati, G., Puglia, G., Sartori, G. and Terenghi, G. - J. Chem. Soc. Perkin I 1862 (1980).