

## NOTE

### AN IMPROVED METHOD FOR PREPARING TRITIUM LABELED FLUOXETINE

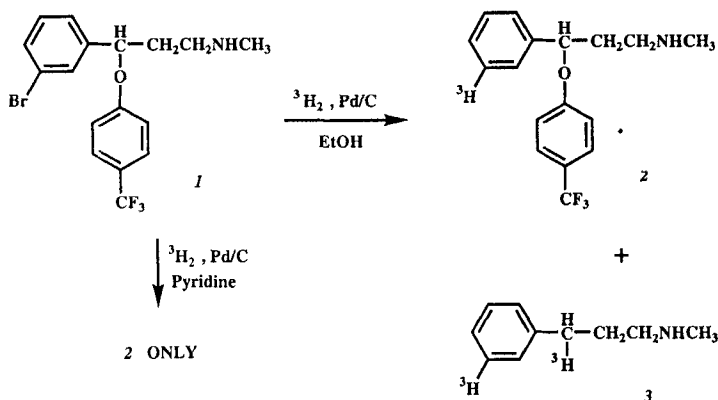
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#### SUMMARY

Palladium-on-charcoal catalyzed reduction of N-methyl-3-(3-bromo)phenyl-3-(4-trifluoromethyl)phenoxypropylamine (**1**) with tritium gas produces a mixture of the debrominated product [<sup>3</sup>H]fluoxetine (**2**) and N-methyl-3-[<sup>3</sup>H]phenylpropylamine(**3**), which results from cleavage of the benzylic carbon-oxygen bond. Carrying out this reaction in the presence of pyridine eliminates hydrogenolysis and produces [<sup>3</sup>H]fluoxetine as the sole product.

**Key Words:** Tritiation, Palladium-on-charcoal, Pyridine, Reduction, Hydrogenolysis, Inhibition, Fluoxetine

We recently had occasion to require tritium labeled fluoxetine (**2**) for conducting toxicological studies with an antioxidant anti-inflammatory compound. [<sup>3</sup>H]fluoxetine had been previously prepared by catalytic reduction of the bromo derivative **1** (**1**) with tritium gas in the presence of Pd-C in EtOH. However, the reaction was accompanied by extensive hydrogenolysis of the benzylic carbon-oxygen bond, which led to the dephenoxyated product N-methyl-3-phenylpropylamine (**3**). In our hands, the reaction could not be effectively controlled, and **3** was either the predominant or exclusive product. It was recently reported that catalytic hydrogenolysis of benzyl ethers could be inhibited by the addition of an amine to the reaction mixture (**2**). Accordingly, we carried out the reduction of **1** with tritium gas in pyridine, which proved to



be an effective mediator of the competing debromination and hydrogenolysis reactions. In pyridine, **1** was smoothly reduced with tritium gas in the presence of 5% Pd-C to produce exclusively **2**. No trace of the hydrogenolysis product **3** was detected in the reaction mixture by HPLC. With this procedure, we obtained [<sup>3</sup>H]fluoxetine with specific activity of 28.7 Ci/mmol. <sup>3</sup>H-NMR showed presence of a single tritiated species. Subsequent to this work, we have found that inclusion of amines in palladium catalyzed reduction mixtures could also influence protium/tritium exchanges at benzylic positions. These findings have been utilized to effect regiospecific tritiations of benzylic ether containing compounds of biological interest, which will be reported elsewhere.

### EXPERIMENTAL PROCEDURE

A solution of 19.4 mg of **1** (0.05 mmol) in 1 mL of pyridine was stirred at room temperature with 10 mg of 5% Pd-C catalyst under carrier-free tritium gas at an initial pressure of 475 torr (3). Gas uptake ceased after 15 min at 450 torr. The reaction was terminated after a total of 60 min. After removal of labile tritium with repeated alternate addition and vacuum distillation of 1 mL portions of methanol, the reaction mixture was dissolved in methanol and filtered to remove catalyst and concentrated at reduced pressure. The residue

with specific activity of 28.7 Ci/mmol was quantified by liquid scintillation counting (1.44 Ci) and analyzed by HPLC and  $^3\text{H}$ -NMR (320 MHz, in  $\text{CD}_3\text{OD}$ , with TMS, single proton-tritium decoupled singlet at 7.44 ppm). A portion of this crude material was purified by means of preparative HPLC (Zorbax SB C-18 5  $\mu\text{m}$  4.6 mm I.D. X 250 mm column, 375:625:1 V/V  $\text{CH}_3\text{OH}:\text{H}_2\text{O}:\text{TFA}$  mobile phase pumped isocratically at 1 mL/min). The collected purified material showed a single component by HPLC analysis with UV (254 nm) and radioactivity detection, which had identical retention time as an authentic sample of unlabeled fluoxetine.

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#### REFERENCES

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2. Sajiki H. - Tet.Lett. **36**: 3465 (1995).
3. Tritiation reaction was carried out in collaboration with H. Morimoto at the National Tritium Labeling Facility, Lawrence Berkeley Laboratories, University of California at Berkeley.