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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 [^{3}H]fluoxetine (*2*) and N-methyl-3-[3-^{3}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 [^{3}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. [^{3}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 dephenoxylated 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

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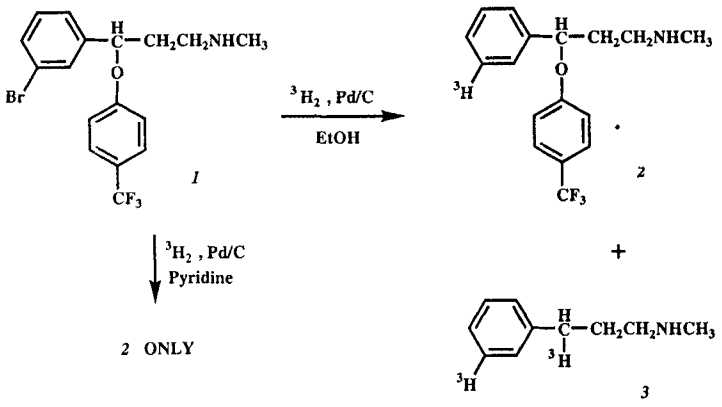

be an effective mediator of the competing debromination and hydrogenolysis reactions. In pyridine, ***1*** was smoothly reduced with tritium gas in the presence of 5% Pd-C to produce exclusively ***2***. No trace of the hydrogenolysis product ***3*** was detected in the reaction mixture by HPLC. With this procedure, we obtained [^{3}H]fluoxetine with specific activity of 28.7 Ci/mmol. ^{3}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}H-NMR (320 MHz, in CD_3OD, 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 µm 4.6 mm I.D. X 250 mm column, 375:625:1 V/V CH_3OH:H_2O: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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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.