PREPARATION AND PURIFICATION OF ^{125}I-LABELED IODOSPIROPERIDOL

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SUMMARY

Iodine-125 labeled spiroperidol has been synthesized by a simple, one-step procedure starting from spiroperidol. This synthesis employs $^{125}I^-$ and H_2O_2 in buffered acetic acid. This pH dependent reaction affords iodospiroperidol in 40% radiochemical yield and a specific activity, after HPLC purification, of ca. 1900 Ci/mmol.

KEY WORDS: Radioiodination, [^{125}I]Iodospiroperidol, Dopamine Receptor

INTRODUCTION

Our search for a readily synthesizable, high specific activity dopamine antagonist, suitable for use in *in vitro* assays, led us to consider the gamma-emitting dopamine antagonist *p*-[^{125}I]iodospiroperidol. Preliminary binding studies with iodospiroperidol indicate that this compound binds with an affinity comparable to spiroperidol itself (1). On this basis, it was felt that this spiroperidol analogue would satisfy our requirements for a high affinity dopamine receptor probe.

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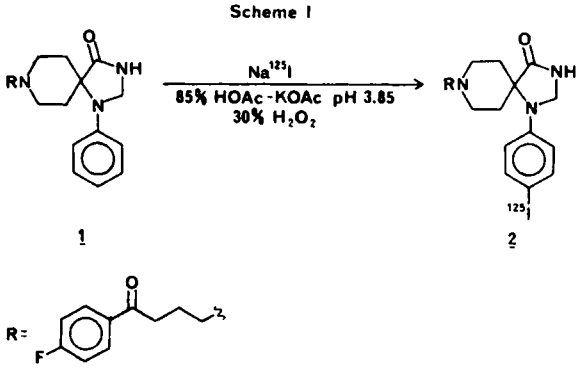
Spiroperidol itself (1) has been labeled with a variety of isotopes including the positron-emitting nuclides carbon-11 and fluorine-18 (2,3). The p-bromo analogue of spiroperidol has also been labeled with bromine-77 (4). The ultimate goal of this work has been to synthesize high specific activity material suitable for assessing in vivo and in vitro dopamine receptor distribution via external imaging. Unfortunately, access to and synthesis with these nuclides is very limited. Iodine-125 labeled spiroperidol thus appeared, for our purposes, to be an attractive alternative.

RESULTS AND DISCUSSION

The title compound was prepared as shown in Scheme I. Spiroperidol (1) was treated with no-carrier-added sodium [^{125}I]iodide in a 2:1 mixture of 85% aqueous acetic acid (buffered to pH 3.85 with potassium acetate) and 30% hydrogen peroxide. After two hours at room temperature and HPLC purification, the desired p-[^{125}I]iodospiroperidol (2) was isolated in 39% radiochemical yield. This yield is much less than 80% yield (based on iodide) which was obtained in model studies using 0.1 equivalent of unlabeled iodide. This method of H_2O_2 oxidation is similar to that used by Katzenellenbogen (5) and Friedman (4) for the electrophilic bromination with bromine-77 of

Scheme I



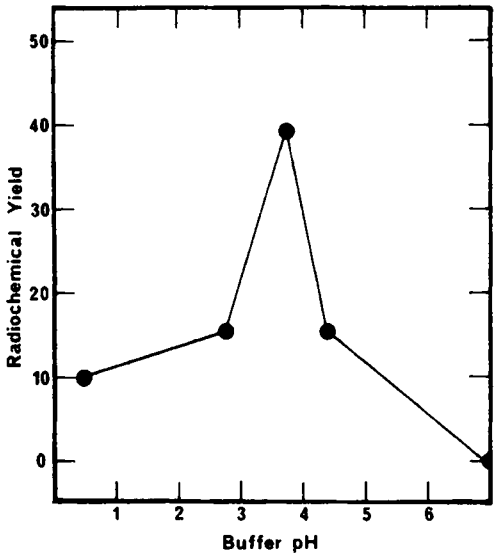


Figure 1. Dependence of the radiochemical yield of iododspiroperidol on buffer pH.

estradiol and spiroperidol respectively. Introduction of iodine-125, however, requires careful control of buffer pH (Figure 1). Reactions run with buffer at a pH of less than the optimal 3.85 show increasingly poorer yields. In fact, when the reaction is run with glacial acetic acid, the radiochemical yield drops to 10%. Similary, use of more basic buffer solutions result in poor yields of iodospiroperidol. At pH 7, where phosphate buffer is substituted for potassium acetate buffer, no incorporation of radioiodine is observed.

Unlike the method of Friedman (4), only a single stage HPLC purification of the radiohalogenated product is necessary to achieve high radiochemical purity and specific activity. This is due to the small amount of spiroperidol used as starting material (300 μg) and the easy separation of unreacted spiroperidol from iodospiroperidol (Figure 2). High specific activity is also assured since reactions run under radioiodination conditions, but without

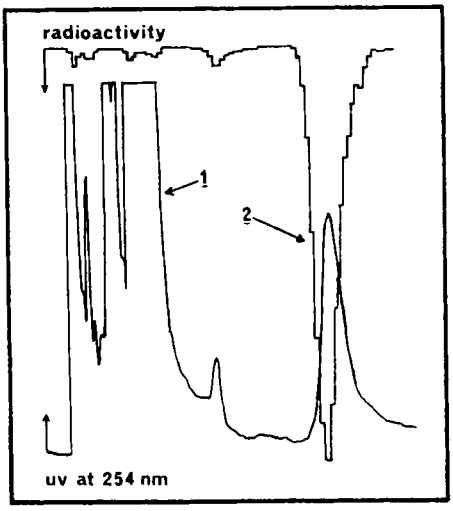


Figure 2. HPLC purification of [^{125}I]iodospiroperidol (2). Note separation of product from unreacted spiroperidol (1).

radioiodide, show no contaminating UV peaks under the iodospiroperidol elution window. Thus, radiochemical purity is 99% and specific activity approaches the theoretical maximum of 2170 Ci/mmol. In the course of this work oxidation with chloramine-T (CAT) was also investigated. Model studies in aqueous THF/HCl show only 21% yields of iodospiroperidol. Similar results are obtained when using acetic acid. In both cases, yields are variable. These reactions are further complicated by the apparent formation of p-chlorospiroperidol as evidenced by the appearance of a slightly more polar peak in the HPLC which is seen in only the CAT reactions and which does not disappear upon deletion of iodide from the reaction mixture. Thus, peroxide oxidation is preferable to CAT oxidation.

CONCLUSION

A simple, one-pot procedure for the *in situ* oxidation of $^{125}I^-$ and its introduction into spiroperidol has been developed. This reaction consistently

gives the desired product in reasonable yield, provided pH is carefully controlled, and affords material of high purity and specific activity.

EXPERIMENTAL

Sodium [^{125}I]iodide in 0.1 N sodium hydroxide and Biofluor liquid scintillation cocktail were purchased from New England Nuclear. Acetic acid-potassium acetate buffer was prepared by dissolving 26.86 g potassium acetate in 85% aqueous acetic acid (pH 3.85). Spiroperidol was obtained as a special research gift from Janssen Pharmaceutica Inc.

High pressure liquid chromatography (HPLC) was performed with a 25 cm x 4.6 mm LiChrosorb RP-18 silica gel column (5 μm C-18 silica gel) eluted with 55:45 0.2 N NH_4OAc/EtOH. Elution was at 0.8 mL/min with UV monitoring at 254 nm. Radioactivity was measured by liquid scintillation counting on a Tracor Analytic Mark III liquid scintillation counter using Biofluor as scintillant or with a Capintec CRC-12 dose callibrator.

Specific activity was determined by UV peak area based on an external iodospiroperidol standard. Radiochemical purity (RCP) was determined by reinjecting a small portion of the final purified product into the HPLC. RCP is the ratio of radioactivity eluting with authentic product to total activity injected. Alternatively, RCP may be determined by spotting 1 μL of radiolabeled compound on top of 1 μg cold compound on a plastic-backed TLC plate without UV indicator (100 μm silica gel, Kodak #13179). After development in 9:1 $CHCl_3$/MeOH and visualization with iodine, the plate is cut into 0.5 cm strips and the radioactivity is counted. RCP is the percentage of total counts eluting with the authentic spot.

p-[^{125}I]Iodospiroperidol. Spiroperidol (300 μg, 0.76 μmol) was dissolved in 0.1 mL aqueous HOAc/KOAc buffer. To this was added 8.12 mCi sodium [^{125}I]iodide in 17 μL 0.1 N NaOH followed by 50 μL 30% H_2O_2. The

reaction mixture was left standing at room temperature 2 h. A saturated $Na_2S_2O_4$ solution (1 mL) was added to the reaction and the mixture extracted with 3 x 1 mL portions of ether. The combined organic extracts were dried by passage through a pipet filled with granular Na_2SO_4. This gave 4.03 mCi (50%) in the organic phase. This was blown down to dryness under a stream of dry argon and the crude product (3.50 mCi) taken up in 55:45 0.2 N NH_4OAc/EtOH. A 1.56 mCi portion of this was purified by HPLC giving 1.41 mCi of p-[^{125}I]iodospiroperidol (total radiochemical yield is 39%).

Analysis of the final product showed it to be 99.1% radiochemically pure and to have a specific activity of 1882 ± 188 Ci/mmol. The product may be stored in the HPLC solvent mixture at 0°.

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