Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIX, No. 3

Synthesis of 5-(2,3-Ditritiopropoxy)-3-(1,2,5,6-tetrahydropyrid-4-yl)indole ([^{3}H]CP-96,501): A Selective Ligand for the Serotonin (5-HT$_{1B}$) Receptor

John E. Macor[§], Carol A. Burkhart[§], Lorraine A. Lebel[§], B. Kenneth Koe[§], Phillip M. Chalabi[Ω], James C. Windels[Ω], and Robert W. Roth[Ω]

[§]Central Research Division, Pfizer Inc., Groton, CT 06340

and [Ω]Chemsyn Laboratories, 13605 W. 96th Terrace, Lenexa, Kansas 66216

SUMMARY

The synthesis of [^{3}H]CP-96,501 [5-(2,3-ditritiopropoxy)-3-(1,2,5,6-tetrahydropyrid-4-yl)indole], a selective radioligand for the serotonin (5-HT$_{1B}$) receptor and analog of RU-24,969, is described. 5-Hydroxyindole is converted in two steps to 5-(2-propenyloxy)-3-(N-t-butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)indole (3). Hydrogena-tion or tritiation of 3 followed by removal of the t-butoxycarbonyl protecting group afforded CP-96,501 (1a) and [^{3}H] CP-96,501 (1b), respectively.

Key Words: CP-96,501, 5-propoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole, serotonin, 5-HT$_{1B}$ receptor, tritium, radioligand

INTRODUCTION

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implication in disorders of mood, sexual behavior, feeding and sleeping behavior.[1] However, the study of central nervous system (CNS) serotonin receptors has been hampered by the lack of specific pharmacological tools.[2] Since there are three major groups of serotonin receptors (5-HT$_1$, 5-HT$_2$, and 5-HT$_3$), each with individual subtypes (i.e. 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_{1D}$),[3] there is a constant need for new, receptor-selective tools with which the characteristics of the individual serotonin receptors can be studied. Historically, only the 5-HT$_{1A}$ receptor has had a specific agonist and radioligand: 8-OH-DPAT [(8-hydroxy-2-(N,N-di-*n*-propylamino)tetralin]. The development of 5-HT$_{1A}$ partial agonists for the treatment of depression and anxiety can be seen partially as a result of information about the 5-

0362–4803/91/030249–09$05.00

Received August 6, 1990
Revised October 15, 1990

HT_{1A} receptor derived from this specific agonist. Recently, we have developed a rotationally restricted analog of the potent 5-HT_{1A}/5-HT_{1B}/5-HT_{1D} receptor agonist, RU-24,969 [5-methoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole]. This compound, CP-93,129 [3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one], binds exclusively to the 5-HT_{1B} receptor,[4] and it has been labelled with tritium to afford the first 5-HT_{1B} receptor selective radioligand.[5] However, since [^{3}H]CP-93,129 contains only a single tritium, the need still exists for a more active 5-HT_{1B} receptor radioligand, especially for use as an audioradiographic tool for visualizing 5-HT_{1B} receptors. Therefore, this paper describes the synthesis of [^{3}H]CP-96,501, a direct analog of RU-24,969 with high selectivity for the 5-HT_{1B} receptor and high specific activity (51 Cu/mmol).

TABLE 1 - Binding Affinity of RU-24,969 and CP-96,501 for Serotonin Receptor Subtypes

($X \pm$ SEM, [n] denotes number of experiments)

	IC_{50} (nM)				
Compound	5-HT_{1A}	5-HT_{1B}	5-HT_{1C}	5-HT_{1D}	5-HT_2
RU-24969	14±7 [5]	2.0±0.9 [5]	290±60 [6]	39±4 [3]	5400±2000 [4]
CP-96,501	92±28 [5]	1.5±0.8 [4]	> 1000 [2]	53± 12 [3]	> 10000 [3]

RU-24,969 [5-methoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole] has been claimed as a selective agent for the 5-HT_{1B} receptor,[6] although its specificity is only moderate (approximately 7x, Table 1). We have discovered that extension of the C5-alkoxy sidechain from methyl to propyl increases selectivity for the 5-HT_{1B} receptor from 7x to over 60x versus the 5-HT_{1A} receptor and from 20x to 35x versus the 5-HT_{1D} receptor (Table 1). As a result of these findings, we desired a radiolabelled version of 5-propoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole (CP-96,501) for the selective study of 5-HT_{1B} receptors. In this report, we outline the synthesis of [^{3}H]CP-96,501.

RESULTS AND DISCUSSION

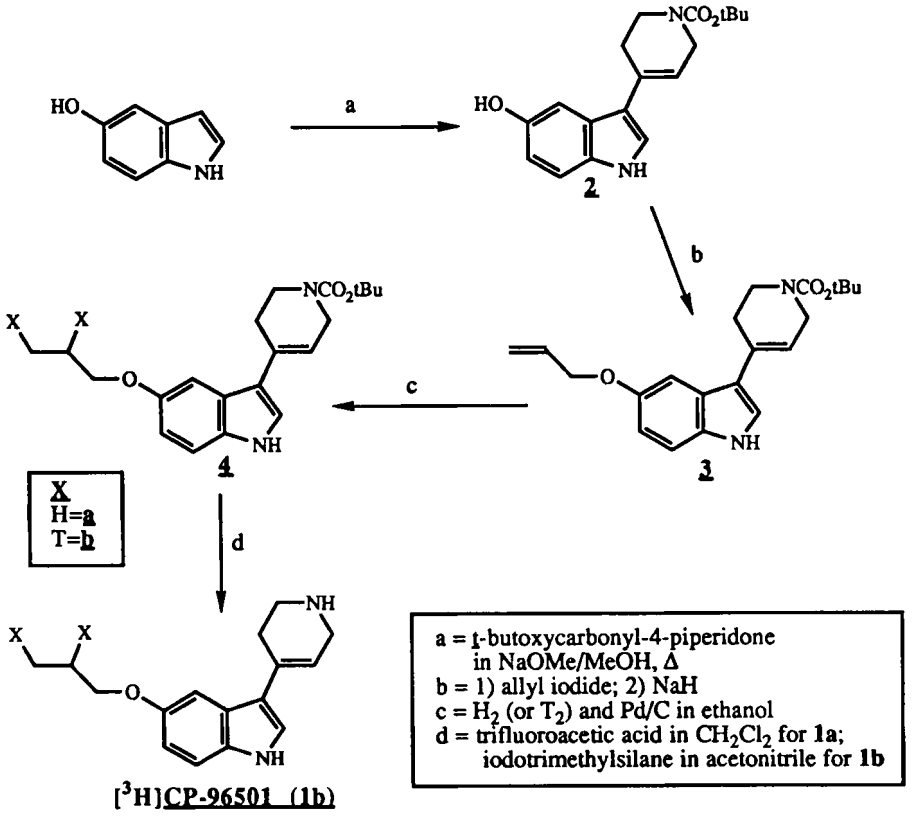
The synthesis of [^{3}H]CP-96,501 ([^{3}H] 5-propoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole) was seen as arising from the tritiation of an olefin located in the C5-alkoxy sidechain. Scheme 1 outlines the formation of [^{3}H]CP-96,501 using this approach. The reaction of 5-hydroxyindole with

N-t-butoxycarbonyl-4-piperidone was analogous to previous reactions of indoles with piperidones,[7] forming the 3-tetrahydropyridylindole derivative (2) in good yield (88%). The relative insolubility of 2 led to easy purification without the use of column chromatography. Deprotonation of the 5-OH on 2 led to rapid decomposition of the anion, so that alkylation of the C5-phenoxide with even active alkylating agents (i.e. allyl iodide) led to significant decomposition of 2 and a poor yield of 3 (39%). To avoid this problem in our case, a solution containing both 2 and allyl iodide was treated with sodium hydride; as the C5-phenoxide formed, it was almost immediately quenched with the active alkylating agent leading to the synthesis of 3-(N-t-butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)-5-(2-propenyloxy)indole (3, 61%). Unfortunately, this modification of conditions for the alkylation of 5-hydroxyindoles applies only when highly activated alkylating agents are used. Although not attempted, the use of Mitsunobu conditions[8] for the alkylation of 5-hydroxyindoles would probably be a more generally applicable reaction.

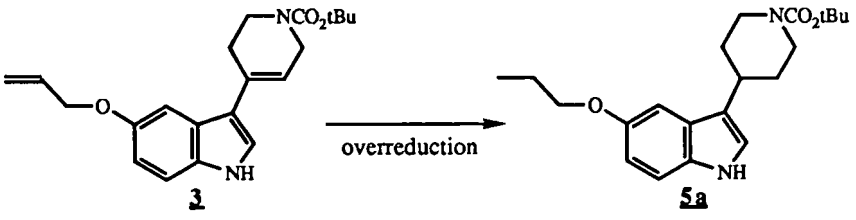
The hydrogenation (tritiation) of the alkene (3) was troublesome. While reduction of the terminal olefin in the 5-(2-propenyloxy) sidechain occurred more rapidly than hydrogenation of the tetrahydropyridyl olefin, the difference in rate between the two reductions was not great enough to form cleanly the desired mono-reduced species (4). Therefore, careful monitoring of the hydrogenation (tritiation) via TLC was necessary to optimize the yield of the desired 5-propoxy-3-tetrahydropyridylindole (4a). If the hydrogenation (tritiation) was not carefully monitored, large amounts of the undesired 3-piperidylindole (5a) were obtained (Scheme 2).

Carefully monitored tritiation of 3 afforded crude 4b (60% of radioactive material) which was used directly. Deprotection of 4 to afford CP-96,501 (1) could be accomplished using either trifluoroacetic acid in methylene chloride or trimethylsilyl iodide in acetonitrile. Use of the latter conditions converted crude 4b to crude [^{3}H]CP-96,501 (1b). Purification of [^{3}H]CP-96,501 (1b) was accomplished using reverse phase HPLC to afford the radioligand (1b) in >98% radiochemical purity with an activity of 51 Ci/mmol. [^{3}H]CP-96,501 was found to be unstable in the presence of oxygen; storage of the radioligand (1b) in aqueous methanol/water with 1% (w/v) ascorbate under an argon atmosphere afforded the best stability for the compound.

[^{3}H]CP-96,501 has been used as a selective 5-HT$_{1B}$ radioligand both in an *in vitro* assay for 5-HT$_{1B}$ receptor ligands (without the need for any masking ligands)[9] and in audioradiographic map-



Scheme 1 - Synthesis of [^{3}H] CP-96,501



Scheme 2

ping of 5-HT$_{1B}$ receptors in rats.[10] The results of these and other studies using our novel radioligand for the 5-HT$_{1B}$ receptor ([^{3}H]CP-96,501) will be reported in appropriate forums in the near future.

EXPERIMENTAL SECTION

Binding experiments were conducted by methods previously reported in the literature: 5-HT$_{1A}$ using rat cortex and [^{3}H]8-OH-DPAT;[11] 5-HT$_{1B}$ using rat cortex and [^{3}H]serotonin;[12] 5-HT$_{1C}$

using pig choroid plexus and [^{3}H]mesulergine;[13] 5-HT_{1D} using bovine caudate and [^{3}H]serotonin;[14] 5-HT_2 using rat anterior cortex and [^{3}H]ketanserin.[15] The concentration of radioligand used in competition studies was approximately equal to the K_D of the binding system.

Chemistry: Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer IR-283B Infrared Spectrophotometer, and NMR spectra were recorded on either a Bruker AM-300 (300 MHz) or a Varian XL300 (300 MHz) spectrometer. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Low resolution mass spectra were obtained on a Finnigan 4310 instrument; high resolution mass spectra were obtained on a AEI MS-30 instrument. Elemental analyses were performed at Central Research Division, Pfizer, Inc., Groton, CT. Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich Gold Label tetrahydrofuran (THF). Room temperature (RT) refers to 20 - 25° C.

Radio-TLC scans were obtained with Bioscan Bid 100 and 200 radiochromatogram scanners. Scintillation counting was carried out with a Beckman LS 3801 liquid scintillation counter using Fisher ScintiVerse LC scintillation cocktail. Preparative and analytical high performance liquid chromatography (HPLC) was carried out on a Varian 5560 instrument with a Rheodyne 7125 injector (200 μL loop).

5-Propoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole (CP-96,501, 1a). A solution of **4a** (0.26 g, 0.73 mmol) and methylene chloride/trifluoroacetic acid (1:1, 10 mL) was stirred at room temperature under nitrogen for 2 h. The resultant reaction solution was evaporated under reduced pressure and the residual oil and partitioned between a saturated solution of sodium hydrogen carbonate (10 mL) and ethyl acetate (10 mL). The ethyl acetate layer was removed, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure. The residual solid was triturated with ether to afford **1a** as the trifluoroacetate hydrate (0.18 g, 0.46 mmol, 63%): mp, decomposes 203.0-205.0° C; IR (KBr) 3260, 1675, 1620, 1520, 1480, 1465, 1425, 1205 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.38 (d, J=2.7 Hz, 1H), 7.27 (d, J=9.0 Hz, 1H), 7.24 (d, J=2.3 Hz, 1H), 6.77 (dd, J=2.3 and 9.0 Hz, 1H), 6.09 (br m, 1H), 3.92 (t, J=6.4 Hz, 2H), 3.59 (br m, 2H), 3.13 (t, J=5.7 Hz, 2H), 2.52-2.47 (m, 2H), 1.79-1.69 (m, 2H), 0.99 (t, J=6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 153.1, 132.2, 130.2, 124.8, 123.8, 115.5, 115.5, 112.4, 111.7, 103.4, 69.6, 43.3, 41.7, 26.2, 22.4, 10.6; LRMS (m/z, relative intensity) 257 (30), 256 (M^+, 100), 255 (88), 227 (50), 213 (38), 185 (33), 80 (27); HRMS calcd for

$C_{16}H_{20}N_2O$ 256.1573; found 256.1590 (5.5 ppm deviation, 5 scans). Anal. calcd for $C_{16}H_{20}N_2O \cdot CF_3CO_2H \cdot H_2O$: C, 55.67; H, 5.97; N, 7.21. Found: C, 55.32; H. 5.59; N, 6.88.

5-(2,3-Ditritiopropoxy)-3-(1,2,5,6-tetrahydropyrid-4-yl)indole (CP-96,501, 1b). A solution of crude **4b** (5.2 Ci) in dry acetonitrile (5 mL) was treated with iodotrimethylsilane (60 µL, approx 2 eq) at RT, and the resulting dark red solution was stirred for 1 h under argon at RT after which TLC (LK6F silica; methanol:triethylamine, 9:1) showed complete conversion of **4b** (R_f=0.8) to **1a** (R_f=0.15). Solvent was removed via evaporation under reduced pressure. The residue was taken up in methylene chloride (5 mL) and washed with 5% acetic acid (2 x 5 mL). The aqueous extracts were back-extracted with methylene chloride (5 mL), and the combined methylene chloride extracts were washed with a saturated solution of sodium thiosulfate (5 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue (4.7 Ci) was taken up in methanol under argon with p-di-tert-butyl catechol (5 mg) added. During subsequent manipulations, solutions of crude **1a** were kept under an argon atmosphere at or below 0° C. Purification was carried out by reverse phase HPLC using a Varian 5560 instrument (Rheodyne 7125 injector with a 200 µL loop) with a Whatman Partisil 5 ODS 3 column (4.6 x 250 mm) and 2:3 methanol: 1% acetic acid (pH=4) as the mobile phase (1 mL/isocractic) with UV detection at 263 nm. The product (15.4 min average retention time), which was collected into an ice cold solution of 1% methanolic ascorbic acid, was obtained with >98% radiochemical purity (HPLC) and having a specific activity of 50.5 Ci/mmol by UV spectrophotometry. The product (**1a**) was stored under argon at -70° C in methanol at a concentration of 1 mCi/mL with 1% (wt/vol) ascorbic acid added for stability. Storage of one sample as such resulted in approximately 30% decomposition over 5 weeks.

5-Hydroxy-3-(4-*tert*-butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)indole (2). To a stirred solution of sodium (6.91 g, 300 mmol, 8 equivalents) in absolute methanol (125 mL) were added 5-hydroxyindole (5.00 g, 37.55 mmol) and N-*tert*-butoxycarbonyl-4-piperidone (12.72 g, 63.84 mmol, 1.7 equivalents), and this solution was heated at reflux under nitrogen for 3 h. Before the last hour of reflux, additional N-*tert*-butoxycarbonyl-4-piperidone (2.60 g, 13.04 mmol, 0.34 equivalents) was added. The resulting reaction solution was evaporated under reduced pressure, and the residual solids were partitioned between a saturated solution of sodium hydrogen carbonate (100 mL) and ethyl acetate (100 mL). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). All organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid was triturated in ether (100 mL) to afford **1** (10.36 g,

32.95 mmol, 88%) as an off-white solid: mp decomposes above 230° C; IR (KBr) 3280, 1655, 1640, 1575, 1470, 1435, 1365 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.9 (br d, NH), 8.70 (br s, OH), 7.32 (d, J=2.3 Hz, 1H), 7.18 (d, J=8.6 Hz, 1H), 7.15 (d, J=2.1 Hz, 1H), 6.64 (dd, J=2.2 and 8.6 Hz, 1H), 5.98 (br m, 1H), 4.04 (br m, 2H), 3.55 (br t, J=5.6 Hz, 2H), 2.51-2.47 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 154.0, 151.1, 131.5, 130.5, 125.2, 123.5, 115.4, 114.8, 112.1, 111.5, 104.2, 78.7, 39.2, 38.9, 38.7, 28.2; LRMS m/z (relative intensity) 314 (M^+, 2), 258 (21), 257 (100), 241 (8), 213 (14), 57 (15). Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.73; H, 7.15; N, 8.89.

3-(4-*t*-Butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)-5-(2-propenyloxy)indole (3). To a stirred mixture of 2 (0.63 g, 2.00 mmol) and allyl iodide (0.25 mL, 2.51 mmol, 1.25 eq) in acetone (H_2O < 0.5%, 15 mL) at RT under nitrogen was added sodium hydride (60% dispersion in oil, 100 mg, 2.50 mmol, 1.25 eq) all at once. The resulting reaction solution rapidly became clear and was stirred at RT under nitrogen for 1 h. A saturated solution of sodium hydrogen carbonate (10 mL) was added, and then acetone was removed form the resulting mixture via evaporation under reduced pressure. The residual aqueous mixture was extracted with ethyl acetate (2 x 20 mL), and these extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography of the resulting oil using silica gel (32-64 μm, approx 150 g) and elution with 30% ethyl acetate in hexanes afforded a brown solid which was triturated in ether/hexanes (1:1, 10 mL) to yield 3 (0.43 g, 1.21 mmol, 61%) as an off-white solid: mp 135.0-137.0° C; IR (KBr) 1665, 1650, 1620, 1580, 1525, 1480, 1465, 1455, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.18 (br m, 1H), 7.33 (d, J=2.3 Hz, 1H), 7.24 (d, J=8.4 Hz, 1H), 7.13 (d, J=2.7 Hz, 1H), 6.89 (dd, J=2.2 and 9.0 Hz, 1H), 6.17-6.04 (m, 2H), 5.47-5.39 (m, 1H), 5.30-5.25 (m, 1H), 4.59-4.56 (m, 2H), 4.12 (br m, 2 H), 3.65 (t, J=5.8 Hz, 2H), 2.53 (br m, 2H), 1.51 (s, 9H); ^{13}C NMR δ 155.0, 153.5, 133.9, 132.2, 130.1, 125.4, 122.2, 117.6, 117.4, 113.0, 112.0, 104.5, 79.6, 70.0, 43.8, 41.0, 40.1, 28.5; LRMS (m/z, relative intensity) 354 (M^+, 8), 297 (100), 256 (15), 57 (32). Anal. calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90; found: C, 71.07; H, 7.32; N, 7.78.

5-Propoxy-3-(4-*t*-butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)indole (4a). A mixture of 3 (1.00 g, 2.82 mmol) and 10% Pd/C (0.100 g, 10mol%) in absolute ethanol (35 mL) was stirred under a hydrogen atmosphere (1 atm) at room temperature with careful monitoring of the progress of the hydrogenation by TLC (30% ethyl acetate in hexanes, UV detection). Upon the appearance of the 3-piperidylindole (5a, R_f=0.45) the reaction, hydrogen gas was purged from the reaction. Note that 3

and the desired product (4a) have approximately the same R_f in this TLC system (R_f=0.30). The resultant reaction mixture was filtered through celite, and the filtrate was evaporated under reduced pressure. Column chromatography of the residue using 10-30% ethyl acetate gradient in hexanes afforded first 5a (0.25 g, 0.70 mmol, 25%) as a white solid identical in all respects with the solid obtained via high pressure reduction of 3. Further elution afforded 4a (0.40 g, 1.12 mmol, 40%) as a white solid: mp, 149.0-150.0° C; IR (KBr) 3320, 1670, 1655, 1620, 1580, 1530, 1475, 1440, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (br s, 1H), 7.32 (d, J=2.2 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 7.14 (d, J=2.5 Hz, 1H), 6.88 (dd, J=2.4 Hz and 8.8 Hz, 1H), 6.12-6.06 (br m, 1H), 4.15-4.12 (br m, 2H), 3.97 (t, J=6.6 Hz, 2H), 3.67 (t, J=5.7 Hz, 2H), 2.59-2.49 (br m, 2H), 1.89-1.78 (m, 2H), 1.50 (s, 9H), 1.06 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.1, 153.9, 132.1, 130.3, 125.4, 122.4, 117.2, 112.8, 112.1, 104.1, 79.7, 70.7, 59.7, 43.8, 40.0, 28.6, 22.9, 10.7; LRMS (m/z, relative intensity) 356 (M^+, 9), 300 (36), 299 (100), 297 (39), 283 (15), 255 (31), 57 (59); HRMS calcd for $C_{21}H_{28}N_2O_3$ 356.2099; found 356.2096 (1.1 ppm deviation, 5 scans); Anal. calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86; found: C, 70.26; H, 7.85; N, 7.58.

5-(2,3-Ditritiopropoxy)-3-(4-*t*-butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)indole (4b). A mixture of 3 (59 mg, 0.172 mmol), 10% Pd/C (6 mg) and p-di-tert-butyl catechol (1.2 mg, added as a stabilizer) was taken up in ethyl acetate (6 mL). The solution was degassed in vacuo and stirred under 11.2 Ci (0.19 mmol) of tritium gas at RT. Reaction progress was followed by TLC (LK6F silica; hexane:ethyl acetate, 4:1). Complete conversion of 3 (R_f=0.4) to 4b (R_f=0.5) was observed after 1 h. Radio-TLC analysis indicated that 60% of the total activity conformed to the desired product with the remaining activity corresponding to overreduced material (5b) (R_f=0.55). Catalyst was removed by filtration through celite, and solvent was removed via evaporation under reduced pressure. Labile tritium was eliminated by co-distillation with methanol (3 x 2 mL). The resulting crude product (5.2 Ci) was used directly in the subsequent step without purification.

5-Propoxy-3-(4-piperidyl)indole (5a). A mixture of 3 (0.100 g, 0.28 mmol) and 10% Pd/C (0.010 g, 10 mol%) in absolute ethanol (25 mL) was shaken under a hydrogen atmosphere (3 atm) at room temperature for 2 h. The resulting solution was filtered through celite, and the filtrate was evaporated under reduced pressure to afford 5a (0.100 g, 0.28 mmol, 99%) as a white solid: mp, 129.0-130.0° C; IR (KBr) 3300, 1685, 1660, 1620, 1580, 1470, 1425, 1360, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (br s, 1H), 7.23 (d, J=8.8 Hz, 1H), 7.05 (d, J=2.4 Hz, 1H), 6.91 (d, J=2.4 Hz, 1H), 6.86 (dd, J=2.4 and 8.8 Hz, 1H), 4.34-4.11 (m, 2 H), 3.97 (t, J=6.6 Hz, 2H), 2.98-2.84 (m,

3H), 2.06-1.98 (m, 2H), 1.90-1.78 (m, 2H), 1.70-1.56 (m, 2H), 1.49 (s, 9H), 1.06 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.1, 153.2, 131.7, 126.9, 120.7, 120.4, 112.5, 111.9, 102.4, 79.5, 70.7, 44.6, 33.7, 32.7, 28.6, 22.9, 10.7; LRMS (m/z, relative intensity) 359 (9), 358 (M^+, 43), 302 (27), 257 (25), 215 (17), 202 (28), 159 (23), 82 (23), 57 (100); HRMS calcd for $C_{21}H_{30}N_2O_3$ 358.2255; found 358.2214 (11.7 ppm deviation, 5 scans). Anal. calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81; found: C, 69.99; H, 8.37; N, 7.81.

REFERENCES

1. Glennon, R.A. -- *J. Med. Chem.*, **30**: 1 (1987).
2. Peroutka, S.J. -- *Ann. Rev. Neurosci.*, **11**: 45 (1988).
3. For a review of serotonin receptors and pharmacology see: Schmidt, A.W. and Peroutka, S.J. -- *FASEB Journal*, 2242 (1989), and references cited within.
4. (a) Macor, J.E. and Newman, M.E. -- *Heterocycles*, **31**: 805 (1990); (b) Macor, J.E., Burkhart, C.A., Heym, J.H., Ives, J.L., Lebel, L.A., Newman, M.E., Nielsen, J.A., Ryan, K., Schulz, D.W., Torgersen, L.K., and Koe, B.K.-- *J. Med. Chem.*, **33**: 2087 (1990); (c) Macor, J.E., Burkhart, C.A., Heym, J.H., Ives, J.L., Lebel, L.A., Newman, M.E., Nielsen, J.A., Ryan, K., Schulz, D.W., Torgersen, L.K., and Koe, B.K., presented at the *199th ACS National Meeting*, Boston, Medicinal Chemistry Division, Abstract 15 (1990).
5. Macor, J.E., Ryan, K., Chalabi, P.M., Windels, J.C., and Roth, R.W. -- *Journal of Labelled Compounds and Radiopharmaceuticals*, 1990 (*in press*).
6. Sills, M.A., Wolfe, B.B., and Frazer A. -- *J. Pharmacol. Exp. Ther.*, **231**: 480 (1984).
7. Guillaume, J., Dumont, C., Laurent, J., and Nédélec, L. -- *Eur. J. Med. Chem.*, **22**: 33 (1987).
8. Mitsunobu, O. -- *Synthesis*, 1 (1981).
9. Koe, B.K., Macor, J.E., and Lebel, L.A. -- Presented at *20th Annual Meeting for the Society for Neuroscience*, St. Louis, Missouri, Abstract 427.10 (1990).
10. Seeger, T., Macor, J.E., and Pratt, K. *unpublished results.*
11. Hoyer, D., Engel, G., and Kalkman, H.O. -- *Eur. J. Pharm.*, **118**:13 (1985).
12. Peroutka, S.J. -- *J. Neurochem.*, **47**: 529 (1986).
13. Pazos, A.; Hoyer, D., and Palacios, J.M. *Eur. J. Pharmacol.*, **106**: 539 (1985).
14. Heuring, R.E. and Peroutka, S.J. *J. Neurosci.*, **7**: 894 (1987).
15. Leysen, J.E.; Niemeggers, C.J.E.; Van Neuten, J.M. and Laduron, P.M. *Mol. Pharmacol.*, **21**: 301 (1982).