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THE SYNTHESIS OF [FLUOROPHENYL-^{3}H(N)] OCFENTANIL AND [FLUOROPHENYL-^{3}H(N)] BRIFENTANIL[1]

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SUMMARY

[Fluorophenyl - ^{3}H(N)] Ocfentanil (1b) and [fluorophenyl - ^{3}H(N)] brifentanil (2b) were synthesized by catalytic tritiation of appropriate bromo precursors (1a,2a). The products were purified by preparative HPLC and characterized chromatographically and by proton decoupled ^{3}H NMR.

Key Words: 4-Anilidopiperidine Analgesic, Ocfentanil, Brifentanil, Tritium Labelling Synthesis, ^{3}H NMR.

INTRODUCTION

During the past thirty years the 4-anilidopiperidine class of compounds has provided an increasing number of candidates for clinical trial in the analgesic area and has recently been reviewed.[2] In particular it was noted in structure activity relationship studies that the presence of an ortho-fluorine on the N-phenyl ring increased the potency of the 4-anilidopiperidine analgesics. Two particular compounds, ocfentanil and brifentanil required the preparation of tritiated analogues to assist in pharmacokinetic studies.[3] We now describe the synthesis and characterization of [fluorophenyl -^{3}H(N)] ocfentanil (1b) and [fluorophenyl-^{3}H(N)] brifentanil (2b).

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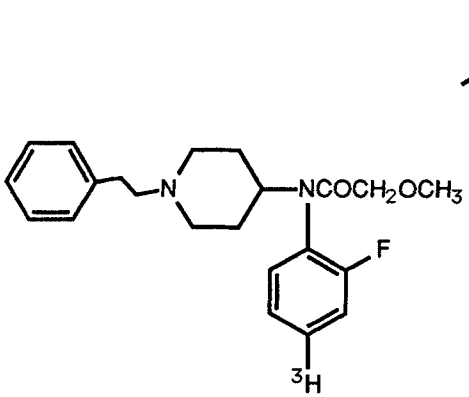
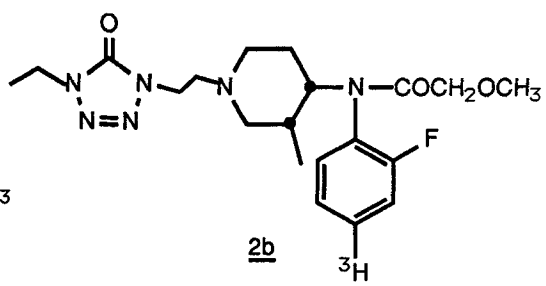
RESULTS AND DISCUSSION

Brominated aromatic compounds have served as extremely useful substrates for tritiation at high specific activity[4]. Brominated analogues of ocfentanil (1a) and brifentanil (2a) were synthesized (as shown in Scheme I) to afford precursors to the respective tritiated radioligands. Precursors 1a and 2a were each catalytically reduced with tritium for several hours in ethanol with a small amount of triethylamine. Following catalyst filtration and labile tritium removal, each crude product was purified by reverse phase HPLC to yield [fluorophenyl-^{3}H(N)] ocfentanil (1b) and [fluorophenyl-^{3}H(N)] brifentanil (2b). Each radioligand was demonstrated to be radiochemically homogeneous on both TLC and HPLC, and cochromatographed with authentic standards. The UV(ethanol) spectra of 1b and 2b were found to be superimposable on those of authentic substances and indicated specific activity values of 21-24 Ci/mmol. Proton decoupled ^{3}H NMR[5] spectra were obtained for each radioligand (Figures 1 and 2) and indicated that a majority of the tritium was incorporated on the fluorophenyl ring of each as demonstrated by fluorine-tritium coupling. In the case of 1b however, about 10% of the tritium also resided on the benzylic position (δ2.70).

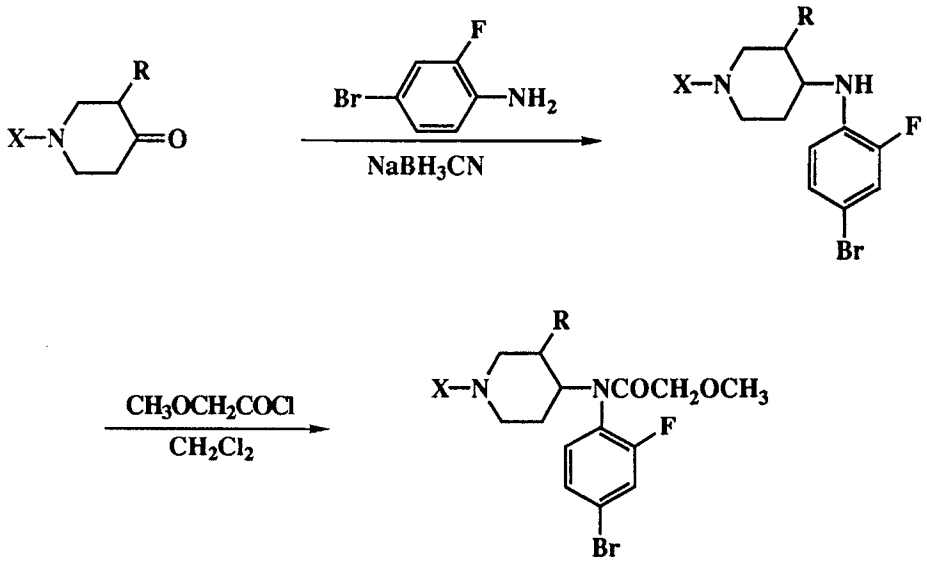


1b

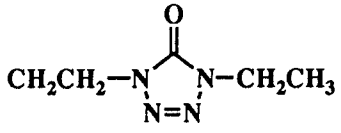


2b

Scheme I: Synthesis of Bromoocfentanil (1a) And Bromobrifentanil (2a)



1a R= H X= CH_2CH_2Ph

2a R= CH_3 X= 

EXPERIMENTAL SECTION

General Methods Evaporations were carried out on a Buchi rotary evaporator in vacuo at bath temperatures below 40°C. TLC was performed on Analtech 5 x 15 cm (250 μm, analytical) silica gel GF coated glass plates using the solvent system $CHCl_3$:CH_3OH (20:1). Autoradiography was performed at 0°C after spraying with PPO (Du Pont, NEN Products) and exposing the TLC plates to Du Pont Cronex x-ray film. TLC plates were also scanned (~ 3 min.) for radioactivity (~10 μCi of sample) by using a Packard 7201 or Bioscan scanner. Analytical HPLC was performed on a Waters instrument using a Zorbax ODS column. Peak detection was performed simultaneously by UV (280 nm - Waters 440 UV detector) and a liquid

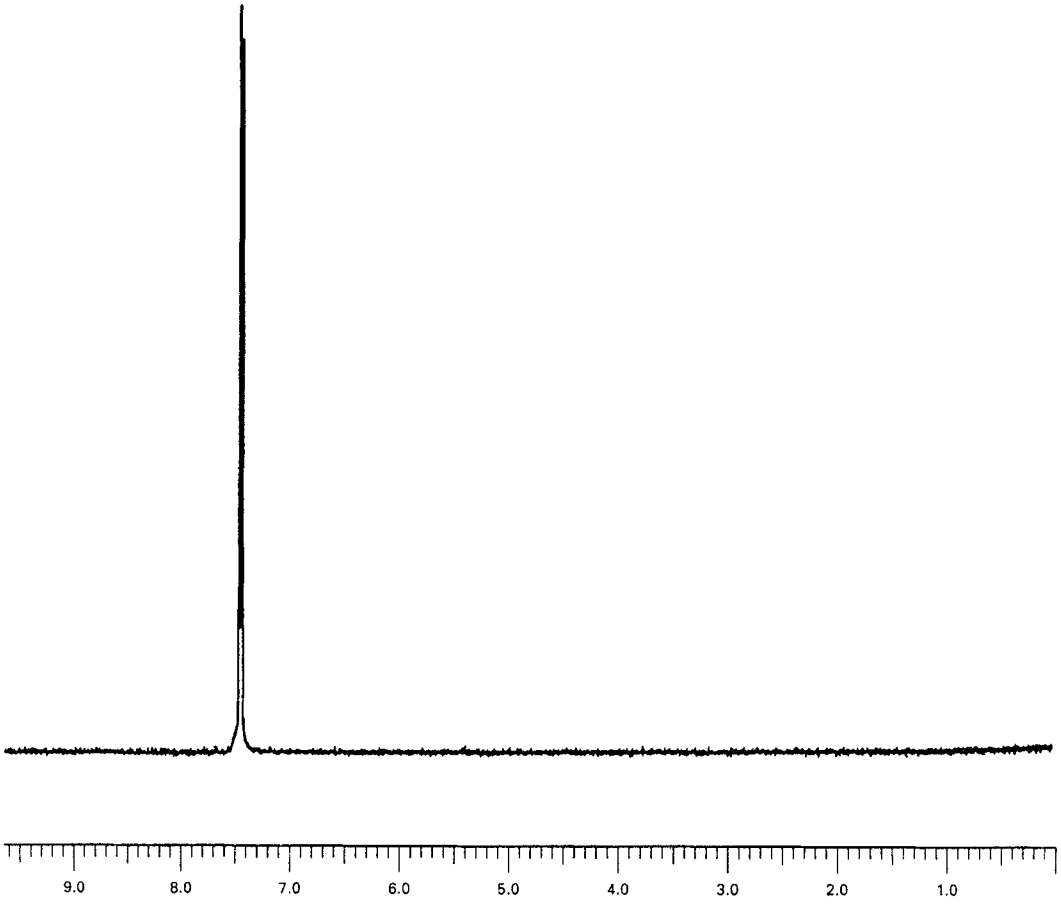


Figure 2: Proton decoupled ^{3}H NMR ($CDCl_3$) of 2b.

scintillation flow monitor. UV spectra were measured on a Beckman Model 25 Spectrophotometer. The proton and triton magnetic resonance spectra were obtained on a Bruker WP 200 mHz NMR spectrometer and chemical shifts are expressed in parts per million (ppm) downfield from internal $(CH_3)_4Si$.

Bromoocfentanil (1a) A mixture of 1-(2-phenethyl)-4-piperidone (9.04 g, 44.4 mmol), 4-bromo-2-fluoroaniline (50.17 g, 264 mmol), $NaBH_3CN$ (2.23 g, 35.5 mmol) and 50 g of 3A molecular sieves in 160 mL of a 0.5M methanolic HCl solution was stirred at room temperature under

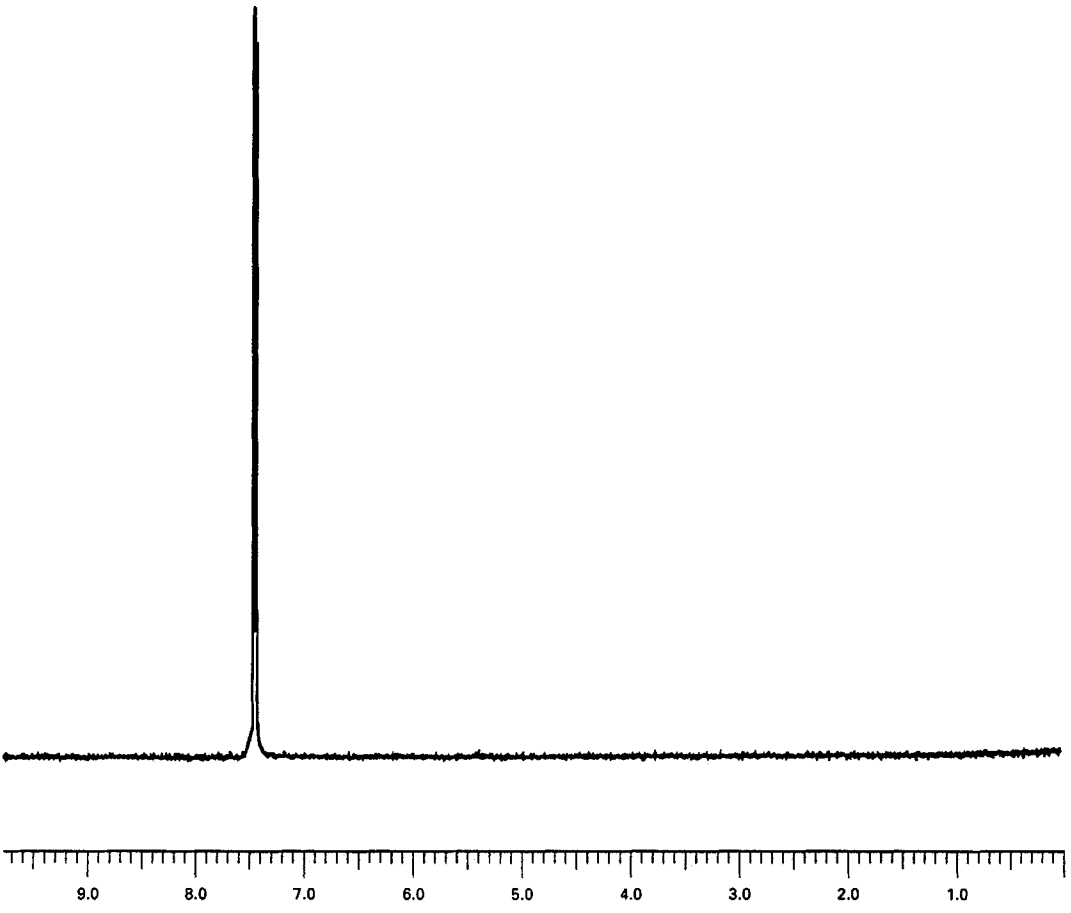


Figure 2: Proton decoupled ^{3}H NMR ($CDCl_3$) of 2b.

nitrogen for 4 days. The molecular sieves were filtered off and the filtrate was evaporated under vacuum to give a solid residue. The residue was dissolved in dilute aqueous NaOH and extracted with CH_2Cl_2 to provide 16 g of a crude product that was chromatographed on a silica gel column eluted with ethyl acetate: hexane (30:70) to afford 7.12 g (43% yield) of 1-(2-phenethyl)-4-(4-bromo-2-fluoroanilino) piperidine as an oil. A solution of this product (6.64 g, 17.6 mmol) and methoxyacetyl chloride (20 g, 184.3 mmol) in 25 mL of CH_2Cl_2 was heated at reflux overnight. The reaction mixture was cooled to room temperature. Cold dilute aqueous NaOH was

added and the mixture was extracted with CH_2Cl_2 to yield a crude product which was filtered through a short silica gel column with ethyl acetate as solvent to afford 7.69 g (97%) of bromoocfentanil 1a (mp 115-116°C). FTIR 1678, 1600 - 1500, 1493, 750 - 702, 605 cm^{-1}

Calcd. for $C_{22}H_{26}N_2BrFO_2$:	C, 58.80; H, 5.83; N, 6.23.
Found:	C, 58.61; H, 5.89; N, 6.50.

[Fluorophenyl-^{3}H(N)] Ocfentanil HCl (1b) A solution of 8 mg (0.018 mmol) of 1a in 0.25 mL of EtOH and 11 µL of Et_3N with 8 mg of 5% Pd/C was reduced with 60 Ci of tritium gas for 3 h at 24°C. Following catalyst filtration and labile tritium removal with CH_3OH, the crude product was dissolved in 30 mL of CH_3OH (total radioactivity = 297 mCi). It was purified by reverse phase HPLC using a mobile phase consisting of 1% aq. triethylammonium acetate (pH 6):CH_3OH (50:50), and the purest fractions were combined. The mobile phase was removed by rotary evaporation and two 5 mL portions of EtOH were also evaporated from the residue. The product was dissolved in 20 mL of EtOH and enough aq. HCl was added to form its HCl salt (total radioactivity = 167 mCi, a 38% radiochemical yield based on 1a). Purified in this way [fluorophenyl-^{3}H(N)] ocfentanil HCl was found to be 99% radiochemically pure by TLC and HPLC (Zorbax ODS -1% aq. triethylammonium acetate (pH 4):CH_3CN (30:20)). In both the TLC and HPLC systems the radioligand cochromatographed with authentic cold standard. The UV (EtOH) of 1b was superimposable on that of cold standard and indicated a specific activity of 24.4 Ci/mmol (where ϵ 265 = 1205 for ocfentanil HCl). A ^{1}H decoupled ^{3}H NMR ($CDCl_3$) of the radioligand was obtained and showed a doublet (J_{F^3H} = 5.27 Hz) at δ7.41 indicating tritium incorporation on the fluorophenyl ring (~ 90% of the total) and singlet at δ2.70 indicating some tritium incorporation into the benzylic position (~10% of total).

Bromobrifentanil (2a) A mixture of 1-benzyl-3-methyl-4-piperidone[6], (21.429 g, 105 mmol) and 20% $Pd(OH)_2$ on carbon (2.428 g) in 100 mL of

EtOH was hydrogenated under 51 psi with a Parr hydrogenator for one day at room temperature. The catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure to yield 3-methyl-4-piperidone (11.315 g, 95% yield). A mixture of this ketone (11.08 g, 98 mmol), 2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl) ethyl bromide (30.30 g, 137.1 mmol), NaI (1.5 g, 10 mmol) and Na_2CO_3 (50 g, 471.7 mmol) in 150 mL of CH_3CN was heated at reflux for 4 days. The mixture was cooled and filtered free of solid. The filtrate was evaporated to dryness under vacuum to yield a crude product which was purified by preparative silica gel HPLC (Waters Prep 500, ethyl acetate) to afford 12.77 g (51% yield) of pure 1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl) ethyl]-3-methyl-4-piperidone as an oil. A mixture of this intermediate (6.4 g, 25.5 mmol), 4-bromo-2-fluoroaniline (32.85 g, 172.9 mmol), $NaBH_3CN$ (1.6 g, 25.5 mmol), HCl gas (2 g, 55 mmol) and 50 g of 3A molecular sieves in 150 mL of methanol was stirred at room temperature for 4 days. The molecular sieves were filtered off and the filtrate was evaporated under reduced pressure to give a residue which was extracted with CH_2Cl_2, dried over Na_2SO_4 and filtered. The filtrate was evaporated and then distilled using a Kugerhor oven (90°C under 0.3 mm Hg) to yield 7.78 g of a dark oil. This was purified by preparative silica gel HPLC (Waters Prep 500, ethyl acetate: hexane (70:30)) to afford 5.22 g (48% yield) of 1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-3-methyl-4-(4-bromo-2-fluoroanilino) piperidine. A portion of this cis, trans mixture (4.5 g, 10.5 mmol) and methoxyacetyl chloride (18. 0 g, 165.8 mmol) in 50 mL of CH_2Cl_2 was heated at reflux for 16 h. The reaction mixture was then poured into ice and made basic with dilute aqueous NaOH. The mixture was extracted with CH_2Cl_2, and the combined extacts were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness under vacuum to yield an oily residue. It was purified by preparative silica gel HPLC (Waters Prep 500, ethyl acetate) to afford 2.04 g (38.8% yield) of bromobrifentanil 2a (cis isomer: R_f=0.28 on silica gel eluted with ethyl acetate; the trans isomer (R_f=0.22 in the same TLC system) could also be recovered from the purification in 50.6% yield.) FTIR 1720, 1681 cm^{-1}.

Calc'd for $C_{20}H_{28}N_6O_3BrF \cdot HCl$: C, 44.83; H, 5.46; N, 15.68
Found: C, 45.06; H, 5.43; N, 15.50

[Fluorophenyl-^{3}H(N)] Brifentanil HCl (2b) A solution of 15 mg (0.03 mmol) of 2a in 0.35 mL of EtOH and 13 μL of Et_3N with 15 mg of 5% Pd/C was reduced with 60 Ci of tritium gas for 3 h at 24°C. Following catalyst filtration and labile tritium removal with CH_3OH, the crude product was dissolved in 50 mL of CH_3OH (total radioactivity = 575 mCi). It was purified by reverse phase HPLC using a mobile phase consisting of 1% aq. triethylammonium acetate (pH 6):CH_3OH (50:50), and the purest fractions were combined. The mobile phase was removed by rotary evaporation and two 5 mL portions of EtOH were also evaporated from the residue. The product was dissolved in 30 mL of EtOH and enough aq. HCl was added to form its HCl salt (total radioactivity = 200 mCi, a 31% radiochemical yield based on 2a). Purified in this way [fluorophenyl-^{3}H(N)] brifentanil HCl was found to be 99% radiochemically pure by TLC and HPLC (Zorbax ODS - aq. 10 mmol triethylammonium acetate (pH 6):CH_3OH (80:20)). In both the TLC and HPLC systems the radioligand cochromatographed with authentic cold standard. The UV (EtOH) of 2b was superimposable on that of authentic cold standard and indicated a specific activity of 21.3 Ci/mmol (where ϵ 265 = 1065 for brifentanil HCl). A ^{1}H decoupled ^{3}H NMR ($CDCl_3$) of the radioligand was obtained and showed a doublet (J_F3_H = 5.27 Hz) at δ7.42 indicating exclusive tritium incorporation on the fluorophenyl ring.

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