Synthesis of 7-^{3}H-(1S, 4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride (7-^{3}H-Sertraline)

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Summary

The preparation of the title compound, a selective serotonin uptake inhibitor with antidepressant properties in man, is described. The preparation of the 7-bromo precursor via a stereoselective seven-step sequence from (1R)-7-bromo-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine is described. The radiochemical purity of the product obtained after reduction with tritium was greater than 99 % and the specific activity was 17.6 Ci/mM.

Key words: ^{3}H-Sertraline, ^{3}H-CP-51,974-01, Antidepressant, 5-HT Uptake Inhibitor.

Introduction

(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride (1, sertraline, CP-51,974-01) has been shown to be a highly selective and potent competitive inhibitor of synaptosomal serotonin uptake[1]. Such agents may exhibit antidepressant activity in man unaccompanied by anticholinergic or cardiovascular side effects often seen with more traditional forms of antidepressant therapy. Since compound 1 is among the most potent and selective agents known to inhibit 5-HT reuptake and since it has little or no effect on the uptake of other neurotransmitters, it seemed to be an ideal agent for the study of the uptake site through radioligand binding. This communication describes the synthesis of tritiated sertraline of high specific activity by hydrogenolysis of an aromatic bromine atom from an optically pure precursor with tritium gas.

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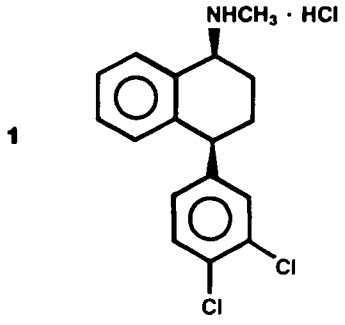

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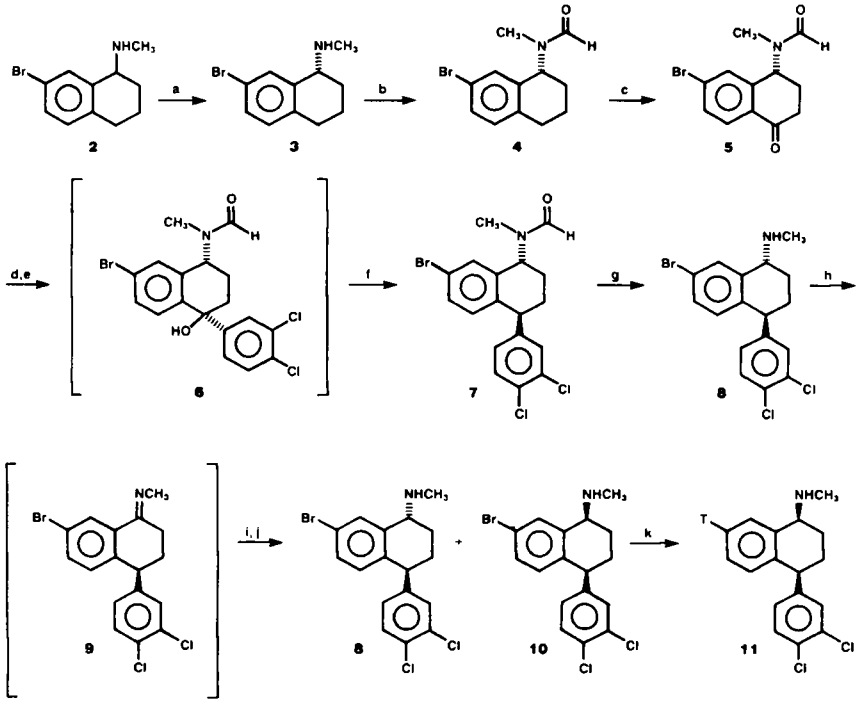
The synthesis of this labelled compound was complicated by the fact that sertraline is a single enantiomer of the the IS,4S configuration[2] and thus a resolution step must be incorporated into the synthesis and by the fact that many processes for synthesis of this agent employ a catalytic hydrogenation step at some point[3]. To address these issues, the synthesis outlined in Scheme I was devised. This process was initially carried through on racemic material. However, it was found to be very difficult to resolve the racemic bromine-substituted cis amine at the end of the synthesis and an early resolution to furnish compound 3 was ultimately utilized in the successful preparation of optically pure 12.

Scheme I



2 3 4 5 6 7 8 9 8 10 11

a) N-Acetyl-D-phenylalanine, EtOH; b) Ac_2O, HCOOH, CH_2Cl_2; c) $KMnO_4$, H_2O/acetone; d) 3,4-$Cl_2C_6H_4MgI$, ether/toluene; e) H^+, H_2O; f) Et_3SiH, BF_3, CH_2Cl_2; g) 4:1 2-propanol/conc. HCl; h) NaOCl, $NaOCH_3$, CH_3OH/H_2O; i) $NaBH_4$, CH_3OH, THF; j) column chromatography; k) T_2, 5% Pd/C, $N(CH_2CH_3)_3$, THF.

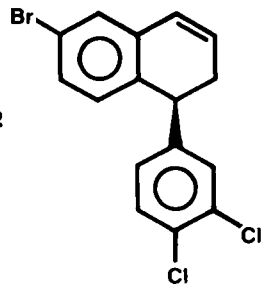
Results

The choice of the 7-position for the label was based on several considerations. First, metabolic studies have shown that demethylation at nitrogen and/or oxidation and hydrolysis to the tetralone is a facile process[4]. Further metabolism at positions 2 and/or 3 has been observed as well as potential exchange at C-4. Second, no metabolites in the aromatic ring of the naphthyl moiety have yet been detected and third, the starting 7-bromo-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine 2 could readily be prepared from known 7-bromo-1,2,3,4-tetrahydronaphthalene-1(2H)-one[5].

Resolution of compound 2 was achieved with either N-acetyl-tyrosine or N-acetyl-phenylalanine, the latter being preferred for reasons of availability as well as a more favorable solubility profile of the diastereoisomeric salts. Salts from N-acetyl-phenylalanine were fine needles unsuitable for x-ray analysis but fortunately the N-acetyl-L-tyrosine salt formed large single crystals from methanol and could be utilized for determination of absolute configuration by single crystal x-ray analysis[6]. The enantiomers derived from the N-acetyl-phenylalanine salts were then correlated by TLC analysis of the diastereoisomeric amides formed with (+)-Mosher's acid chloride. In this way, enantiomeric purity of >99% could be assured.

Protection of compound 3 at nitrogen with mixed formic-acetic anhydride gave the formamide 4 in quantitative yield. Oxidation of 4 could be accomplished best with $KMnO_4$ in aqueous acetone. Yields of 40-45% in this step were acceptable since good recovery of unreacted starting material was possible. Reaction of the ketone 5 with 3,4-dichlorophenyl magnesium iodide gave the carbinol intermediate 6 which was isolated in the racemic sequence and upon which a single-crystal x-ray analysis was also performed[6], demonstrating that the product from this transformation was cis with regard to the aryl and formamide substituents. In the optically active sequence, this compound was submitted to the ionic hydrogenation[7] step without purification, giving the optically active trans N-formyl derivative 7 in 41% isolated yield for the two steps. In the ionic hydrogenation step, inversion at C-4 occurs quantitatively, as the only product detected from this reaction is the trans enantiomer 7. The choice of the R enantiomer in starting material 3 thus ultimately dictates the 4S absolute stereochemistry of 7.

Acidic hydrolysis of 7 gave the trans 1R,4S amine 8 in 58% yield as its HCl salt. Little or no elimination to the 3,4-dihydronaphthalene 12 was seen in this procedure when the N-protecting group is formyl. The acetamide and benzamide derivatives gave substantially more of compound 12 under these conditions.



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Compound 8 possesses the skeletal features of 7-bromo sertraline including the 4S configuration of the 3,4-dichlorophenyl group but is IR by virtue of the starting material 3. Inversion at C-I was achieved by mild oxidation of 8 with hypochlorite in base to give the imine 9. This intermediate could be reduced *in situ* with sodium borohydride to give a 1:1 mixture of compounds 8 and 10, which are readily separable by column chromatography. Reduction of 10 with hydrogen under mild conditions and formation of the HCl salt gave sertraline identical in all respects, including optical rotation, with that prepared by other synthetic routes.

Reduction of 10 with tritium gas under similar conditions gave, after purification, 7-^{3}H-sertraline 11 which was purified by HPLC[9]. The specific activity of this product was found to be 22.7 Ci/mmol. This product was suitable for a variety of biological and biochemical assays, the results of which will be reported at a later date.

Experimental

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian T-60, and EM-390 and XL-300 spectrometers. IR spectra were determined on a Perkin-Elmer Model 283B infrared spectrophotometer. Low and high resolution mass spectra were obtained with a Finnigan Model 4510 mass spectrometer and an AEI MS-30 instrument respectively. Microanalyses were performed by the Pfizer Analytical Department. Column chromatography was performed by the flash method on 32-63 micron silica gel. Specific rotations were determined using a Perkin-Elmer Model 241 MC polarimeter.

Resolution of 7-bromo-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine 2. A solution of 33.12 g (0.16 mol) of N-acetyl-L-phenylalanine in 500 mL of hot abs. EtOH was mixed with a solution of 38.4 g (0.16 mol) of compound 2 in 250 mL of abs. EtOH. Upon cooling, crystals of the undesired diastereomeric IS salt deposited. The mother liquors were evaporated and

partitioned between 10% NaOH solution and ether to give, after drying and evaporation of solvent, 20.4 g of oil enriched in the 1R enantiomer. This oil was dissolved in 180 mL of abs. EtOH and was mixed with a solution of 17.60 g (85.0 mmol) of N-acetyl-D-phenylalanine in 500 mL of boiling abs. EtOH. The solution was scratched to induce crystallization and was then cooled slowly overnight. The crystals were isolated by filtration and washed with abs. EtOH and ether to give 29.89 g of salt, mp 191-193 °C. This product was recrystallized from 800 mL of abs. EtOH and isolated in the same way to give 26.43 g of salt, mp 191-193 °C, $[a]_D^{22}$ = -64.6° (c = 1, CH_3OH). The salt was converted to 14.28 g of oily free base by partitioning between 10% NaOH solution and ether, drying, and evaporation of the solvent. A small aliquot was converted to the HCl salt (3 HCl) for analysis, mp 255-257 °C, $[a]_D^{22}$ = -55.2° (c = 1, CH_3OH).

Preparation of (1R)-7-bromo-N-formyl-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine 4. Acetic-formic anhydride (prepared by treating 26.2 mL (0.278 mol) of acetic anhydride with 13.1 mL (0.349 mol) of 98% formic acid at 0-5 °C) was added dropwise to a 0-5 °C solution of 14.28 g (0.059 mol) of compound 3 in 13.1 mL of 98% formic acid and 10 mL of CH_2C1_2. The reaction mixture was stirred 2 h at room temperature and then the volatiles were removed in vacuo. The residues were dissolved in ether and extracted with excess aqueous $NaHCO_3$ solution, water and dilute HCl solution. The organic extracts were dried ($MgS0_4$) and evaporated to give 16.20 g (102%) of an oil which was sufficiently pure for use in the next step. The analytical sample crystallized from ether/hexane, mp 63-65 °C, $[a]_D^{22}$ = + 14.0° (c = 1, CH_3OH).

Preparation of (4R)-6-Bromo-4-(N-formyl-N-methylamino)-3,4-dihydro-1(2H)-naphthalenone 5. A solution of 10.26 g (0.038 mol) of compound 4 in 400 mL of acetone was treated with 12.0 g (0.10 mol) of anhydrous $MgS0_4$ and cooled to 10 °C. Then a solution of 6.04 g (0.038 mol) of $KMnO_4$ in 100 mL of H_20 was added dropwise below 10 °C. The resulting solution was stirred 6 h at room temperature. Then a second equal portion of $MgS0_4$ was added followed by a second equal portion of aq. $KMnO_4$ solution. This reaction mixture was stirred overnight at room temperature.

Precipitated MnO_2 was filtered off and washed with acetone and EtOAc. The organic solvent was removed by evaporation and the aqueous suspension remaining was extracted with ethyl acetate. The combined extracts were dried ($MgS0_4$) and evaporated and the residue was dissolved in the minimum amount of ether and scratched. The crystalline solid which formed was filtered and washed with ether to give 3.00 g (28%) of the desired product, mp 120.0-121.5 °C, $[a]_D^{22}$= +46.5° (c = I, acetone).

The mother liquors were chromatographed using 9:1 EtOAc/hexane as eluent to give an additional 1.57 g of product (total 42%) and 3.35 g (33%) of recovered starting material.

Preparation of (1R,4S)-7-Bromo-4-(3,4-dichlorophenyl)-N-formyl-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine 7. A Grignard reagent was prepared by addition of 11.47 g (42.0 mmol) of 3,4-dichloroiodobenzene in a few mL of ether to 1.05 g (43.4 mmol) of magnesium metal in ether. This reaction mixture was kept below 5 °C while a solution of 7.90 g (28.0 mmol) of compound 5 in 200 mL of dry toluene was added dropwise. A tan precipitate formed. This mixture was stirred overnight at room temperature.

The reaction mixture was decomposed with 200 mL of 10% NH_4Cl solution and the separated organic layer was washed with water and then dilute HCl solution until the aqueous layer was clear. Then the organic layer was dried ($MgSO_4$) and evaporated to give 11.65 g of the crude carbinol product 6.

This oil was dissolved in 500 mL of CH_2C1_2 and 10 mL of Et_3SiH and the solution, under dry N_2, was cooled to -40 °C in a dry ice/acetone bath. BF_3 (g) was bubbled into the reaction mixture for 20 min and then the reaction mixture was allowed to warm slowly to room temperature.

Excess BF_3 was purged into a trap with dry N_2 and then anhydrous K_2C0_3 and water were added. The separated CH_2Cl_2 layer was washed with brine and this solution was combined with two ether extracts of the aqueous layer, dried and evaporated to give 10.26 g of oily product mixture. This was chromatographed using 1:1 hexane/EtOAc as eluent to give 4.74 g (41%) of the desired product 7 as a white foam, $[a]_D^{22}$ = + 61.6° (c = 1, CH_30H).

(1R,4S)-7-bromo-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride 8. A solution of 4.65 g (11.3 mmol) of compound 7 in 140 mL of 2-hydroxypropane was treated with 35 mL of conc. HCl and heated at reflux for 3.5 h. The reaction mixture was then cooled and the solvents were evaporated. The residues were partitioned between ether and 10% NaOH and the aqueous phase was extracted twice with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated and the residues were dissolved in 10 mL of acetone and treated with HCl (g) in ether. After stirring overnight, the crystalline product was filtered and washed with dry ether to give compound 8 as its hydrochloride salt, 2.75 g (58%), mp 254-256 °C, $[a]_D^{22}$ = + 4.3° (c = 1, CH_30H).

(1S,4S)-7-bromo-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride 10. A solution of 0.466 g (20.3 mmol) of sodium in 75 mL of methanol was cooled to 15 °C and 2.75 g (6.76 mmol) of compound 8 (hydrochloride salt) was added. Then 9.7 mL of 5.25% NaOCl solution was added dropwise over about 10 min. The reaction mixture warmed to 22 °C during the addition and a gummy precipitate separated. This was stirred at room temperature for 15 min and then 25 mL of anh. THF was added. Excess $NaBH_4$ was added portionwise over 1 h until disappearance of the imine was observed (TLC in 5:1 hexane/EtOAc). The reaction mixture was then poured into water and extracted four times with EtOAc. The organic extracts were dried ($MgSO_4$) and evaporated and the residues were chromatographed on 130 g of silica gel using 9:1 EtOAc/CH_3OH as eluent to give pure 1S, 4S enantiomer 11 which was dissolved in a few mL of acetone and treated with HCl (g) in ether to give the hydrochloride salt, 703 mg (25%), mp 280-281 °C (dec), $[a]_D^{22}$ = + 58.2° (c = 1, CH_3OH). Mixed fractions and recovered 1R,4S enantiomer 8 (both of which could be recycled) accounted for 54% of the product (total yield 79%, based on recovered starting material).

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