MULTIPLE TRITIUM LABELLING OF (+)-7-CHLORO-8-HYDROXY-1-PHENYL-3-METHYL-2,3,4,5-TETRAHYDRO-1H-3-BENZAZEPINE (SCH23390)

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SUMMARY

We previously reported the synthesis of the antidopaminergic-antipsychotic agent SCH23390 labelled with tritium in the 9 position of the benzazepine ring system at a specific activity of 5.6 Ci/mmole as the racemic mixture. Here, we report the preparation of the higher specific activity (+)-isomer of SCH23390 labelled with tritium in both aromatic rings as well as the N-methyl group. Multiple labelling was achieved by reductive debromination with carrier-free tritium gas of a dibrominated N-normethyl derivative over 5% Pd/C and subsequent N-methylation with high specific activity methyl iodide. The specific activity obtained for the Nor-SCH23390 was 8.8 Ci/mmole and 93.8 Ci/mmole for the SCH23390.

Keywords: (+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine, (+)-7-chloro-8-hydroxy-1-phenyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, palladium catalysis, deuterium, tritium, SCH23390

INTRODUCTION

Recent receptor binding studies,[1,2] using (±)-[9-^{3}H]SCH23390[3] have suggested that this dopaminergic benzazepine derivative, once thought to be the first selective D_1 dopamine antagonist, may actually be interacting with two or more subpopulations of D_1 dopamine receptors.[4] The racemic tritiated product previously prepared in our laboratory[3] had a specific activity of 5.6 Ci/mmole. Since the dextro isomer demonstrates far greater pharmacological activity than the levo isomer and a higher specific activity was desired in order to perform further biochemical and autoradiographic studies, we prepared (+)-[^{3}H]SCH23390 labelled in both aromatic rings as well as the N-methyl group at a specific activity of 93.8 Ci/mmole (326 mCi/mg). Also obtained from this synthesis as the immediate precursor to the (+)-[^{3}H]SCH23390 was the (+)-[^{3}H]N-nor-SCH23390 at a specific activity of 8.8 Ci/

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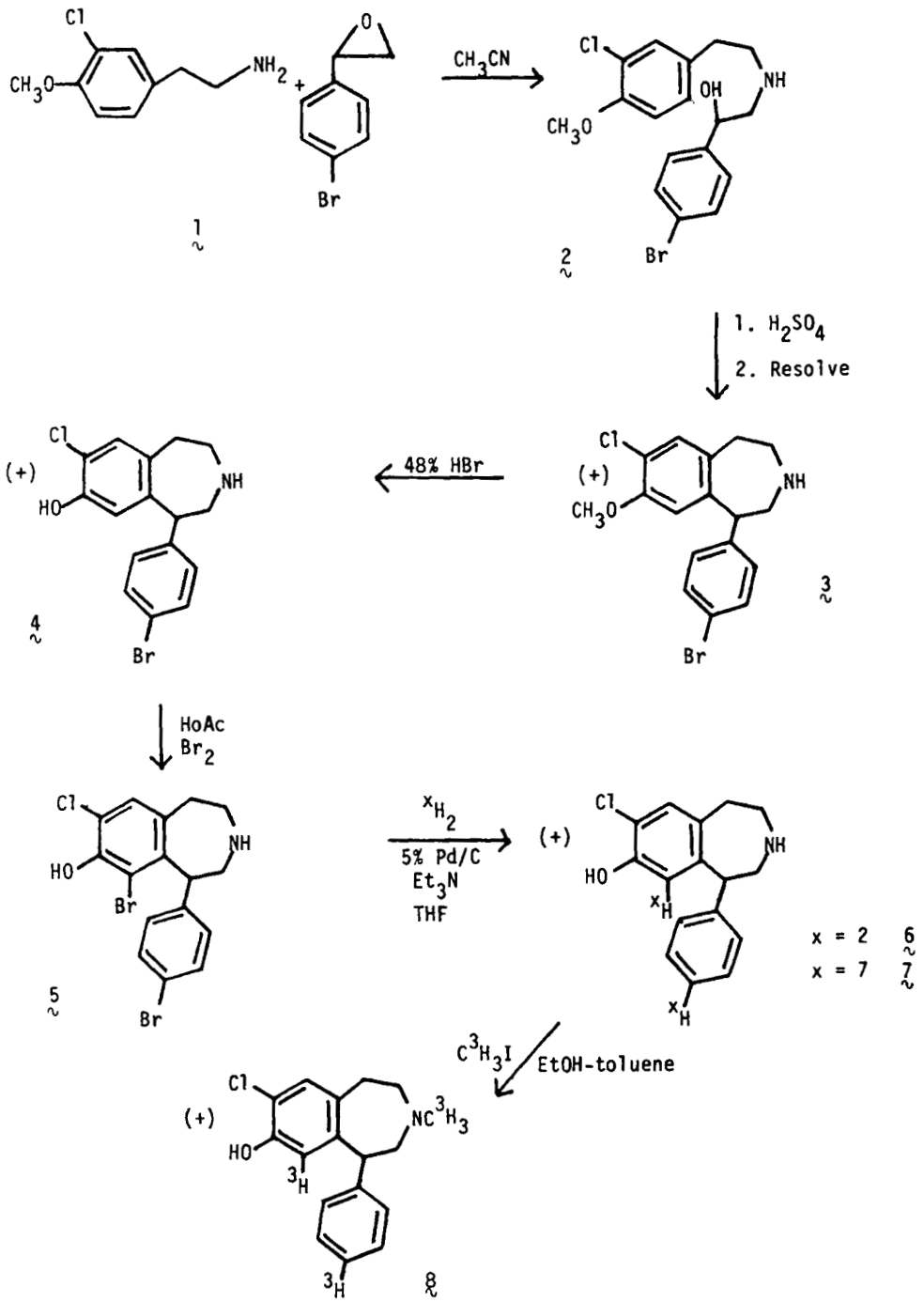
Figure 1


Cl
CH3O
NH2
O
Br
1
CH3CN
OH
NH
2
1. H2SO4
2. Resolve
(+)
HO
48% HBr
3
4
HoAc
Br2
5
xH2
5% Pd/C
Et3N
THF
6
7
x = 2
x = 7
C3H3I
EtOH-toluene
NC3H3
3H
8

mmole (33 mCi/mg) which is also to be utilized for biological studies in our group. The (+)-[^{3}H]SCH23390 was prepared by Pd/C catalyzed reductive debromination of the corresponding (+)-9,13-dibrominated N-normethyl derivative with tritium gas followed by N-methylation with C^3H_3I.

DISCUSSION

We have previously demonstrated the lack of reactivity of the aryl chlorine in SCH23390 toward hydrogenolysis under deuteration and tritiation conditions.[3] Therefore, debromination of an aryl dibromide precursor 5 followed by N-methylation with high specific activity methyl iodide appeared attractive for the preparation of higher specific activity SCH23390. The synthetic scheme of Gold and Chang[5] was employed except that 4-bromostyrene oxide instead of styrene oxide was reacted with the amine 1 to afford the aryl brominated aminoalcohol 2. Ring closure to the racemic benzazepine nucleus 3 was affected with concentrated H_2SO_4. When resolution was first attempted via the N-acetyl-D-leucine salt as reported for the nonbrominated derivative,[5] crystallization of the salt was never achieved even with a variety of organic solvents. Therefore, the (+)-camphor-10-sulfonic acid salt was prepared and recrystallized from CH_3CN-MEOH(4:1) to afford the (+)-isomer of 3 in 81% enantiomeric purity (Figure 1). Subsequent O-demethylation with 48% HBr and aryl bromination with Br_2/HoAc as described earlier[3] afforded the (+)-9,13-dibromo-N-normethyl SCH23390 (5) which would serve as the precursor to the tritiated (+)-SCH23390 as well as the (+)-N-normethyl derivative. Exposure of 5 to 1.0 atm of deuterium gas in the presence of 5% Pd/C afforded the dideuterated product 6. However, mass spectral analysis of deuterium incorporation indicated considerable isotopic dilution had occurred probably involving the active hydrogens on the oxygen and nitrogen atoms (d_0= 50.68%, d_1=40.54% and d_2=8.63%). Upon exposure of 5 to 5.0 Ci of carrier-free tritium gas under similar conditions, 195 mCi of 98% radiochemically pure 7 was obtained with a specific activity of 8.8 Ci/mmole (33 mCi/mg) indicating a 57% improvement in specific activity over our previous procedure. An N-methylation model reaction using unlabelled 6 and 1.0 equivalent of methyl iodide in methanol at room temperature for 24 h afforded (+)-SCH23390 in 66% yield. The analogous reaction of 7 with C^3H_3I (specific activity = 85 Ci/mmole, Amersham) afforded 6.0 mCi of (+)-[^{3}H]SCH23390 at a specific activity of 93.8 Ci/mmole

(326 mCi/mg). As indicated by this yield, the product at this high specific activity is extremely unstable toward handling such as chromatography (see Experimental Procedures).

EXPERIMENTAL PROCEDURES

All chemicals were used as received from the manufacturer. Melting points were obobtained on a Mel-Temp apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a JEOL FX-60 MHz FT spectrometer using TMS as a reference. Radiopurity was determined using a Bioscan BID 100 Image Analyzer. Tritium was counted using a Packard Minaxi 4000 Series Liquid Scintillation Counter (external standard) with Scintiverse® (Fisher) counting solution. Silica gel plates (UV) were used for analytical and preparative work. A Cary 15 ultraviolet spectrometer was used for specific activity determination. Elemental compositions of novel compounds were determined by high resolution mass spectrometry using an AEI MS-902 mass spectrometer. Optical rotations were obtained using an Autopol III automatic polarimeter.

(±)-N-[2-(4-Bromophenyl)-2-hydroxyethyl]-3-chloro-4-methoxyphenethylamine (2). The procedure of Gold and Chang[5] was used. Compound 1[3] (6.4 g, 0.0344 mol) and 6.9 g (0.0344 mol) of 4-bromostyrene oxide were dissolved and refluxed overnight in 50 ml of acetonitrile. The solvent was evaporated *in vacuo* and the gummy residue column chromatographed on silica gel using CH_2Cl_2-MeOH-NH_4OH(90:10:1) to afford 7.4 g (56%) of a tan solid; mp = 181-183°C. ^{1}H-NMR ($CDCl_3$, TMS) δ 7.65-6.70 [m, 7H, Ar$\underline{H}_7$], 4.62 [m, 1H,-C$\underline{H}$OH], 3.90 [s, 3H, OC$\underline{H}_3$] 3.08-2.50 [m, 6H, (C$\underline{H}_2$)$_3$] and 2.40 [s, 1H, N$\underline{H}$].

(+)-7-Chloro-8-methoxy-1-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (3). The racemic carbinol 2 (7.4 g, 0.019 mol) was added in portions to 60 ml of conc. H_2SO_4 with stirring maintaining the temperature at ≤ 12°C throughout. The dark reaction mixture was then stirred at 8°C for 0.5 h and then at room temperature for 1.5 h. The mixture was poured into 500 g of ice; 100 ml of conc. NH_4OH was added followed by 40 g of solid NaOH maintaining the temperature ≤ 30°C. The gummy precipitate was extracted into CH_2Cl_2, the organic extracts dried (Na_2SO_4) and evaporated *in vacuo* to afford 6.7 g (96%) of light yellow solid. Accumulated crude product from multiple preparations were column chromatographed on silica gel 60 with

CH_2Cl_2-MeOH-NH_4OH (95:5:1) to afford a total of 9.2 g of racemic yellow solid; mp=136-137°C. ^{1}H-NMR ($CDCl_3$,TMS) δ 7.49 [d, 2H, Ar-H's #12, 14], 7.00 [d, 2H, Ar-H's#11, 15], 7.19 [s, 1H, Ar-H#6], 6.50 [s, 1H, Ar-H#9], 4.19 [m, 1H, CH], 3.78 [s, 3H, OCH_3], 3.20-2.50 [m, 6H, $(CH_2)_3$] and 2.27 [s, 1H, NH]. The racemic product (7.7 g, 0.021 mol) and 4.9 g (0.021 mol) of (+)-camphor-10-sulfonic acid were dissolved with heating in 70 ml of CH_3CN-MeOH(4:1). After allowing the solution to cool slowly, the resultant salt precipitate was collected and washed with cold CH_3CN and dried to afford 3.7 g of colorless solid; mp=173-176°C. $[\alpha]_D^{25}$ = +20.5° (c=1, methanol). A second recrystallization from 40 ml of CH_3CN-MeOH(4:1) afforded 1.2 g of colorless needles; mp = 193-195°C. $[\alpha]_D^{25}$ = +28.6° (c=1, methanol). The 1.2 g of resolved salt was stirred vigorously in 0.5 N NaOH and ether for 2 h. The ether phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford 750 mg of colorless solid as free base; mp=160-161°C. $[\alpha]_D^{25}$ = +21.0° (c=1, methanol). In order to determine the enantiomeric purity of the resolved bromo derivative, the bromine was reduced off to produce a known compound[5]. Compound 3 (resolved) (104 mg, 0.272 mmol) and 250 µl of Et_3N in 3.0 ml of dry THF were stirred in the presence of 50 mg of 5% Pd/C under 1.0 atm of deuterium gas at room temperature for 16 h. Isolation and purification of the corresponding debrominated product afforded 83 mg (100%) of a semi-solid. $[\alpha]_D^{25}$ = +23.8°C (c=1, ethanol), (lit.[5] $[\alpha]_D^{25}$ = +38.3°). This indicates an enantiomeric purity for 3 of 81% (+)- isomer.

(+)-7-Chloro-8-hydroxy-1-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (4). A mixture of 630 mg (1.72 mmol) of (+)-3 and 30 ml of 48% HBr were stirred at 100°C for 12 h. The volatiles were evaporated *in vacuo* and the residue partitioned be-CH_2Cl_2 and sat'd $NaHCO_3$. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford 348 mg (57%) of a tan solid; mp=110-112°C. $[\alpha]_D^{25}$ = +29.2° (c=1, acetone). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6,TMS) δ 7.71-6.90 [m, 5H, ArH_5], 6.42 [s, 1H, Ar-H #9], 4.15 [m, 1H, CH], 3.55-2.51 [m, 6H, $(CH_2)_3$] and 2.22 [s,1H, NH].

(+)-7-Chloro-8-hydroxy-9-bromo-1-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (5). To a solution of 340 mg (0.966 mmol) of (+)-4 in 5.0 ml of glacial acetic acid was added a solution of 155 mg (0.966 mmol) of bromine in 1.0 ml of glacial acetic acid dropwise with stirring at room temperature. The bromine disappeared immediate-

ly and after 5 min the volatiles were evaporated in vacuo to afford 344 mg (83%) of a light tan solid which was pure by TLC in CH_2CH_2-MEOH-NH_4OH (90:10:1). mp = 236-240°C. $[\alpha]_D^{25}$ = +41.3° (c=1, DMF). ^{1}H-NMR (DMSO-d_6, TMS) δ 7.51 [d, 2H, Ar-H #'s 12, 14], 7.00 [d, 2H, Ar-H #'s 11, 15], 7.21 [s, 1H, Ar-H #6], 4.83 [m, 1H, CH]. and 3.43-2.32 [m, 6H, $(CH_2)_3$]. m/e = 428.9133 ($C_{16}H_{14}Br_2ClNO$ requires 428.9132.

(+)-7-Chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-[9,13-$^2H_2$(n)]3-benzazepine (6). A solution of 120 mg (0.278 mmol) of 5 and 500 µl of triethylamine in 5.0 ml of dry THF was stirred for 4 h at room temperature in the presence of 100 mg of 5% Pd/C under 1.0 atm of deuterium gas. The catalyst was filtered off through a Celite pipet column and the volatiles evaporated in vacuo. The residue was shaken with CH_2Cl_2- sat'd $NaHCO_3$, the organic layer dried (Na_2SO_4) and evaporated in vacuo to afford 87 mg of a brown gum. Column chromatography on silica gel with CH_2Cl_2-MeOH-NH_4OH (90:10:1) afforded 27 mg (43%) of pure product as a yellow solid; mp = 85-87°C. $[\alpha]_D^{25}$ = +9.8° (c=1, DMF). ^{1}H-NMR ($CDCl_3$, TMS) δ 7.41-6.78 [m, 5H, ArH_5], 6.40 [s, 0.4 H, Ar-H #9)], 4.12 [m, 1H, CH], 2.51-3.45 [m, 6H, $(CH_2)_3$] and 2.20 (s, 1H, NH]. Mass spectral data indicates d_0 (m/e =273) = 50.68%, d_1 (m/e =274) = 40.54% and d_2 (m/e =275) = 8.63%.

(+)-7-Chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-[9,13-$^3H_2$(n)]3-benzazepine (7). A solution of 15.1 mg (0.035 mmol) of 5 and 100 µl of triethylamine in 1.0 ml of dry THF was stirred for 4 h at room temperature in the presence of 10 mg of 5% Pd/C under 5.0 Ci (0.086 mmol) of carrier-free tritium gas. The catalyst was filtered off through a Celite-Na_2SO_4 pipet column and the filtrate diluted with methanol and evaporated in vacuo to afford 565 mCi of crude product. TLC-radioscan indicated 68% radiochemical purity. This material was chromatographed on two 20 x 20 cm x 0.25 mm silica gel 60 plates with CH_2Cl_2-MeOH-NH_4OH (90:10:1) using the dibromo precursor 5 and unlabelled product as reference standards. The appropriate band was scraped into CH_2Cl_2-MeOH (4:1), the silica gel filtered off and the filtrate evaporated in vacuo. The residue was dissolved in 100 ml of absolute ethanol and counted to afford 195 mCi (6.0 mg, 63% chemical yield) of product which was 98% radiochemically pure by TLC-radioscan (CH_2Cl_2-MeOH-NH_4OH 90:10:1). A 10 ml aliquot from the above stock solution was evaporated and the residue

dissolved in 10 ml of methanol and scanned from 330-260 nm in an ultraviolet spectrometer in order to determine the specific activity. The spectrum was identical to that obtained for the unlabelled product (ε = 2508, λ_{max} = 283 nm). The specific activity was determined to be 8.8 Ci/mmol (33 mCi/mg).

(+)-7-Chloro-8-hydroxy-1-phenyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SCH23390). To a solution of the corresponding N-normethyl precursor (40 mg, 0.147 mmol) in 2.0 ml of methanol was added 21 mg (0.147 mmol) of methyl iodide and the reaction was allowed to stand overnight at room temperature. The volatiles were evaporated under a stream of N_2 and the residue partitioned between CH_2Cl_2-sat'd $NaHCO_3$. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford a brown gum which was purified by chromatography on two 20 x 20 cm x 0.25 mm silica gel 60 plates (CH_2Cl_2-MeOH-NH_4OH 90:10:1) affording 28 mg (66%) of a light yellow solid which was identical to the product prepared previously.[3] ^{1}H-NMR (DMSO-d_6, TMS) δ 7.3 [m, 5H, Ar$\underline{H}_5$], 7.13 [s, 1H, Ar-H #6], 6.35 [s, 1H, Ar-H #9], 4.25 [t, 1H, C$\underline{H}$], 3.80-2.42 [m, 6H, ($\underline{CH}_2$)$_3$] and 2.28 [s, 3H, NC$\underline{H}_3$].

(+)-7-Chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-[NC^{3}H$_3$-9,13-^{3}H$_2$(n)]3-benzazepine ([^{3}H]SCH23390) (8). A 25.6 ml (50 mCi, 0.0055 mmol) aliquot of the above ethanolic solution of 7 was concentrated to ~1.0 ml *in vacuo* and added to 100 mCi (0.0018 mmol) of [^{3}H]methyl iodide (85 Ci/mmol, Amersham) in 1.0 ml of toluene. TLC-radioscan analysis of the reaction after standing 16 h at room temperature indicated the major component to be the methylated product as well as excess 7 and minor decomposition products. The reaction volume was reduced to ~1.0 ml under a stream of N_2 in the hood to remove any unreacted [^{3}H]methyl iodide and then taken nearly to dryness *in vacuo*. The residue was immediately column chromatographed on 5.0 g of silica gel 60 with CH_2Cl_2-MEOH-NH_4OH (95:5:1). Extensive decomposition occurred. Subsequent chromatography of this material on two 20 x 20 cm x 0.25 mm silica gel plates with CH_2Cl_2-MEOH-NH_4OH (95:5:1) afforded 6.0 mCi of product which was ~94% pure by TLC-radioscan. The product was stored in 500 ml of absolute ethanol at 4-5°C. The specific activity was 93.8 Ci/mmol (326 mCi/mg).

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