TRITIUM LABELLED (±)-7-CHLORO-8-HYDROXY-3-METHYL-1-PHENYL-2,3,4,5-TETRAHYDRO-1H-3-BENZAZEPINE (SCH23390)

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SUMMARY

The antipsychotic drug, SCH23390, once thought to be the first selective D_1 dopamine antagonist, is now believed to possibly produce its profound antidopaminergic and antipsychotic effects via molecular sites that involve recognition characteristics similar to, or are a subpopulation of the D_1 dopamine receptors. Tritium labelled SCH23390 has been prepared in our laboratory by palladium catalyzed reductive aryl debromination of a brominated precursor with carrier free tritium gas in THF. The product is labelled in the 9-position of the benzazepine ring and a specific activity of 5.6 Ci/mmole was obtained.

Key Words: SCH23390, (±)-7-chloro-8-hydroxy-9-bromo-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine, catalytic reduction, deuterium, tritium.

INTRODUCTION

It is generally believed that most of the actions of antipsychotic drugs may be due to the blockade of dopamine receptors, and that the post-synaptic receptors are crucial to the desired clinical effects. Dopamine receptors have been assigned to two classes -- the D_1 class is linked to stimulation of cAMP synthesis by dopamine, whereas the D_2 class is not.[1] Various pharmacological data were consistent with the idea that it was the D_2 class that mediated both antipsychotic effects in man, and various antidopaminergic behavioral effects in laboratory animals or man.[2-6] According to generally accepted nomenclature first proposed by Kebabian and Calne,[1] data demonstrated that SCH23390 was the first selective D_1 dopamine antagonist.

However, Mailman et al.[7,8] demonstrated that when given either intraperitoneally or intracerebroventricularly, SCH23390 had equal or greater potency

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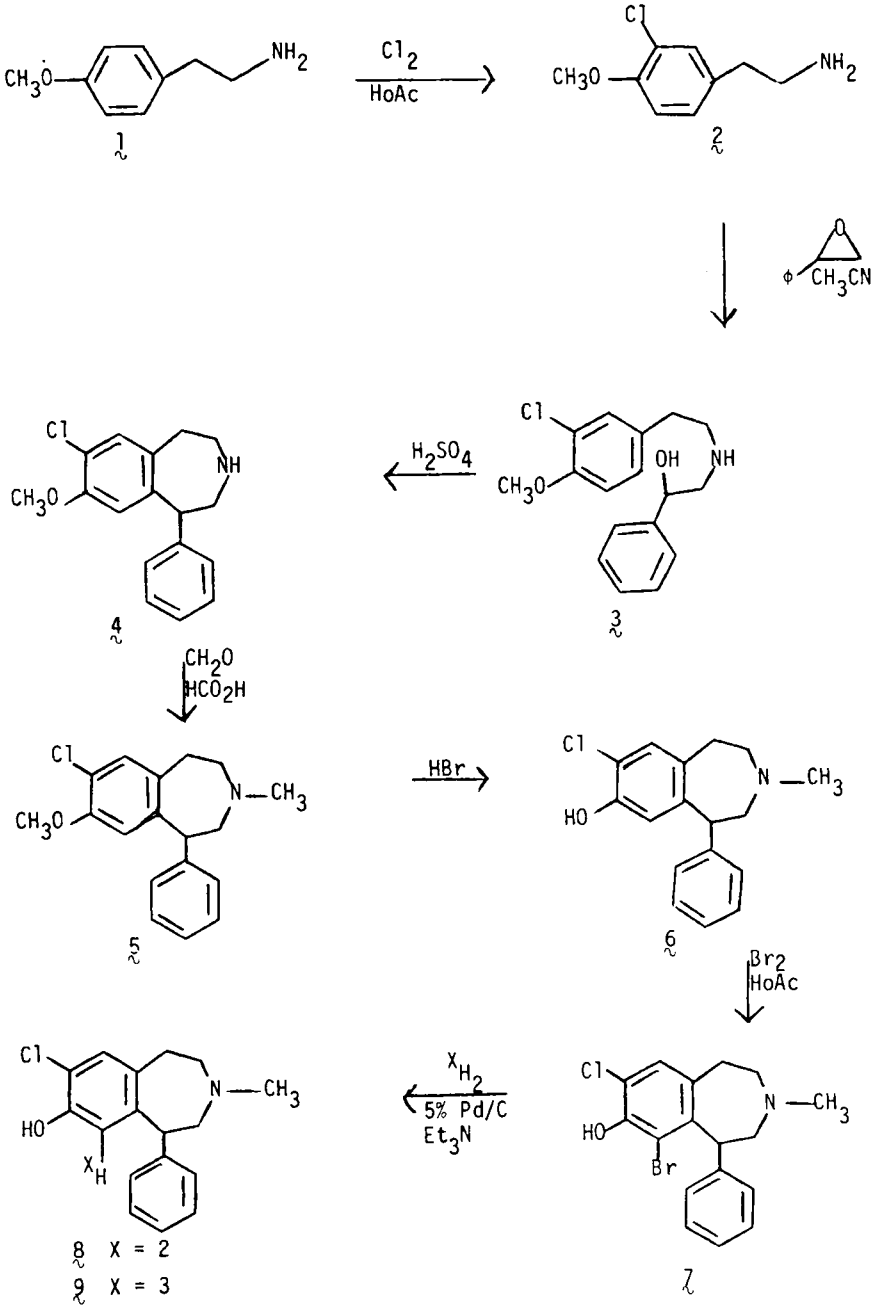
than haloperidol or fluphenazine in antagonizing a variety of behaviors induced by direct-acting or indirect-acting dopamine agonists. It is quite possible that profound antidopaminergic and antipsychotic effects may be mediated by molecular sites that have recognition characteristics similar to, or are a subpopulation of D_1 dopamine receptors. To explore these sites further, the radiolabelled analog of SCH23390 was required. Its use, for characterizing and quantifying behaviorally relevant binding sites, may help resolve issues such as what makes some antipsychotic (neuroleptic) drugs "atypical", and may provide new insights into the neurobiology of dopamine-receptive neurons.

The obvious site for tritium labelling SCH23390 was the N-methyl group obtainable by reaction of the N-normethyl precursor with C^3H_3I. This material has been prepared at a specific activity of ∿50 Ci/mmole,[9] but would be unsuitable for the above studies due to almost certain metabolic demethylation. Therefore, we proposed to tritium label this compound in a nonmetabolic site such as the alkyl or aryl portion of the benzazepine ring system.

DISCUSSION

The most attractive pathway for tritium labelling at first appeared to be the reductive tritiation of the corresponding enamine of SCH23390 as is routinely carried out for suitable cyclic tertiary amino compounds (e.g. tritium labelled morphine analogs). The enamines of such compounds are usually obtainable by Leonard oxidation[10] of the amine in the presence of yellow mercuric oxide in aqueous acetic acid. SCH23390, however, failed to afford any detectable enamine by this procedure. Therefore, as an alternative method, aryl ring labelling via reductive debromination in the presence of Pd/C, Et_3N and tritium gas appeared attractive. Preliminary work to assess the possibility of selectively debrominating in the presence of the aryl chlorine involved subjecting SCH23390 to the prescribed deuteration-tritiation procedure using hydrogen gas at 1.0 atm. No dechlorinated product was detected by TLC or GC after a reaction

FIGURE 1



time of 4 h. Therefore, racemic SCH23390 (6) (Figure 1) was treated with one equivalent of bromine in acetic acid at room temperature to afford the 9-bromo derivative 7 as evidenced by ^{1}H-NMR and mass spectral data. Upon subjecting 7 to 1.0 atm of deuterium gas in the presence of Et_3N, 5% Pd/C and THF, the substrate was rapidly debrominated while leaving the aryl chlorine intact to afford 8. Mass spectral incorporation studies indicated d_0 = 61.19%, d_1 = 36.35%, d_2 = 1.28% and d_3 = 1.18%. Upon tritiation using 5.0 Ci of carrier free tritium gas under similar conditions, 94.3 mCi of pure tritiated product was obtained with a specific activity of 5.6 Ci/mmole (19.4 mCi/mg).

EXPERIMENTAL PROCEDURES

All chemicals were used as obtained from the manufacturer. Melting points were obtained on a Thomas Hoover Melting Point Apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a JEOL FX-60 60 MHz FT spectrometer using either $CDCl_3$ or $(CD_3)_2SO$ (TMS) as solvent. Gas chromatography was performed using a Shimadzu GC-8A chromatograph. Radiopurity was determined using a Packard Radioscanner Model 7201. Tritium was counted using a Packard Liquid Scintillation Counter Model 3255 (internal standard) with Scintiverse R (Fisher) counting solution. Silica gel plates (UV) were used for TLC analyses. Elemental compositions of novel compounds were determined by high resolution mass spectrometry using an AEI MS-902 mass spectrometer and elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona and are correct within ± 0.4% of theory.

3-Chloro-4-methoxyphenethyl amine (2). 4-Methoxyphenethyl amine (1) (39.4 g, 0.261 mol) was dissolved in 300 ml of water and 22 ml of conc. HCl. To this solution was added 20.3 g (0.287 mol) of chlorine gas in 300 ml of glacial acetic acid over a 15 min period maintaining the temperature below 35°C. After standing for 10 min, the volatiles were removed in vacuo and the dark solid residue was dissolved in 100 ml of absolute EtOH and allowed to crystallize at -10°C. The collected precipitate was dissolved in a mixture of 400 ml of satu-

rated $NaHCO_3$ and 400 ml of CH_2Cl_2. The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated in vacuo to afford a dark oil which was distilled (115°C/0.5 mm Hg) (lit.[11] 165°/15mmHg) to afford 19.2 g (41%) of a light yellow oil. ^{1}H-NMR ($CDCl_3$, TMS) δ 7.30-6.70 [m, 3H, ArH_3], 3.88 [s, 3H, OCH_3], 3.1-2.51 [m, 4H, $\phi CH_2CH_2NH_2$], 1.58 [s, 2H, NH_2].

(±)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (± SCH23390) (6). The procedure of Gold and Chang[12] was used. Compound 2 (19.2 g, 0.103 mol) was refluxed 16 h with styrene oxide in acetonitrile to afford 3 in 38% yield; mp = 95-97°C (lit.[12] 95-96°C). Cyclization of 3 in conc. H_2SO_4 afforded 4 in 96% yield as a gum. N-methylation in 37% CH_2O/88% HCO_2H under reflux for 4 h afforded 5 in 68% yield as a gum. O-Demethylation by heating 5 in 48% HBr at 90-100°C for 16 h afforded the racemic product 6 in 49% yield as a colorless solid after recrystallization from absolute ethanol; mp = 216-218°C (lit.[12] for (+)-isomer 188-189°C). TLC, GC and ^{1}H-NMR were identical to an authentic sample. ^{1}H-NMR (CD_3SOCD_3, TMS) δ 7.3 [m, 5H, ArH_5], 7.13 [s, 1H, ArH-6], 6.35 [s, 1H, ArH-9], 4.25 [t, 1H, -CH-], 3.80-2.42 [m, 6H, $-CH_2CH_2N(CH_3)CH_2-$], 2.28 [s, 3H, NCH_3].

(±)-7-Chloro-8-hydroxy-9-bromo-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (7). To a solution of 700 mg (2.44 mmol) of 6 in 10 ml of glacial acetic acid was added dropwise a solution of 429 mg (2.68 mmol) of bromine in 1.0 ml of glacial acetic acid. After stirring 10 min at room temperature, the acetic acid was evaporated in vacuo and the solid residue dissolved in 3.0 ml of warm water. Solid $NaHCO_3$ was added until pH = 8-9 was obtained. The filtered precipitate was recrystallized from ethanol-THF to afford 423 mg (47%) of light yellow solid; mp = 220-221°C. m/e = 365.0182 ($C_{17}H_{17}BrClNO$ requires 365.0183). Anal. C,H,N Theory C = 55.69, H = 4.64, N = 3.82; Found C = 55.74, H = 4.80, N = 3.64. ^{1}H-NMR (CD_3SOCD_3, TMS) δ 7.50-6.91 [m, 6H, ArH_5 + ArH], 4.92 [t, 1H, -CH-], 3.62-2.33 [m, 6H, $-CH_2CH_2N(CH_3)CH_2-$], 2.28 [s, 3H, NCH_3].

(±)-[9-^{2}H]-SCH23390 (8). Brominated SCH23390 (7) (58 mg, 0.158 mmol) and 200 µl of Et_3N in 3.0 ml of freshly distilled THF were stirred for 4 h in the presence of 25 mg of 5% Pd/C under 1.0 atm of deuterium gas at room temperature. The catalyst was removed by filtration through a Celite pipet column and the filtrate evaporated in vacuo to afford a white solid. Column chromatography on silica gel 60 (70-230 mesh) (CH_2Cl_2-MeOH-NH_4OH 95:5:1) afforded 34 mg (73%) of deuterated product as a colorless solid; mp = 213-215°C. Mass spectral data indicated d_0 = 61.19%, d_1 = 36.35%, d_2 = 1.28% and d_3 = 1.18%. ^{1}H-NMR (CD_3SOCD_3, TMS) δ 7.3 [m, 5H, ArH_5], 7.13 [s, 1H, ArH-6], 6.35 [s, 0.6H, ArH-9], 4.25 [t, 1H, -CH-], 3.80-2.42 [m, 6H, -$CH_2CH_2N(CH_3)CH_2$-], 2.28 [s, 3H, NCH_3].

(±)[9-^{3}H]-SCH23390 (9). The brominated compound (7) (22 mg, 0.06 mmol) and 100 µl of Et_3N in 1.0 ml of freshly distilled THF were stirred for 4 h in the presence of 15 mg of 5% Pd/C under 5.0 Ci (0.086 mmol) of carrier free tritium gas at room temperature. The catalyst was removed by filtration through a Celite/Na_2SO_4 pipet column and the filtrate was evaporated in vacuo and the residue dissolved in 10 ml of MeOH and counted to afford 380 mCi of crude product. The MeOH was evaporated in vacuo, the residue dissolved in THF and chromatographed on 2 20 x 20 cm x 0.25 mm silica gel 60 plates (CH_2Cl_2-MeOH-NH_4OH 95:5:1) using authentic SCH23390 as a standard (R_f = 0.75). Removal of the appropriate bands, elution with CH_2Cl_2-MeOH 1:1 and evaporation of the solvent afforded 94.3 mCi (28% chemical yield) of product which was dissolved and stored in 100 ml of absolute EtOH. TLC-radioscan and GC (3% OV-17, 2.0 m, 30 ml/min, 250°C) indicated > 99% radiopurity and > 98% chemical purity, respectively. The specific activity was determined by GC (conditions as stated above) using 4 as an internal standard. The retention time for 9 was 2.1 min and for 4 was 2.5 min. The specific activity was found to be 5.6 Ci/mmol (19.4 mCi/mg). The stock solution was stored at 4°C.

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