PREPARATION OF ^{14}C-LABELED 8,9-DIDEHYDRO-6,8-DIMETHYL-2-METHYLTHIOERGOLINE MESYLATE, A DOPAMINE ANTAGONIST POTENTIALLY USEFUL IN THE TREATMENT OF SCHIZOPHRENIA

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SUMMARY

We have prepared ^{14}C-labeled 8,9-didehydro-6,8-dimethyl -2-methyl-thioergoline mesylate (LY 170542), a dopamine antagonist potentially useful as an anti-psychotic. The ^{14}C-label was introduced via a novel application of the Wittig reaction on 1-(4'-toluene- sulfonyl) -8,9-didehydro-6-methyl-ergolin-8-one and subsequent reduction of 1-(4'-toluenesulfonyl)-17-[^{14}C]-lysergene by lithium/ammonia at -33°C. The 17-[^{14}C]-agroclavine thus prepared was converted into 17-[^{14}C]-LY 170542 by reaction with methanesulfenyl chloride/methanesulfonic acid.

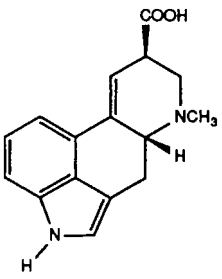
Key Words: carbon-14, LY 170542, anti-psychotic, dopamine antagonist,17-[^{14}C]-agroclavine, Wittig Reaction

INTRODUCTION

Although there are a number of structural types of compounds associated with anti-psychotic properties, the search continues for new drugs useful in the treatment of schizophrenia and other psychoses.[1] Currently available anti-psychotic drugs are frequently unpleasant to take because of unwanted side effects, most of which are extensions of their known pharmacological actions.[2] Some patients stop taking their drugs because of unwanted side-effects. LY 170542 was chosen from a series of ergoline derivatives resulting from a program designed to convert agroclavine (a dopamine agonist) into compounds which possess dopamine antagonist properties.[3] LY 170542 competes with ^{3}H-spiroperidol for binding sites in the rat caudate nucleus and inhibits dopamine -stimulated adenylate cyclase indicating both D_1- and D_2-antagonist activity.[4] Although potentially more active than clorpromazine as an anti-psychotic agent, it is less effective at altering the blood pressure in spontaneously hypertensive rats (suggesting less potential for orthostatic hypotension).[5] In rats, LY 170542 blocked a conditioned avoidance at doses which caused little catalepsy, which may indicate a lower incidence of extra-pyrimidal side effects . Unlike currently available neuroleptics, LY 170542 causes activation of the electroencephalogram in rats and cats rather than depression. This is believed to be an indication of a less sedative profile.[4] The combined pharmacological profile of LY 170542 suggests possible advantages over currently available drugs for the treatment of schizophrenia and related disorders.

0362–4803/88/060667–08$05.00

Received July 7, 1987
Revised October 20, 1987



LYSERGIC ACID

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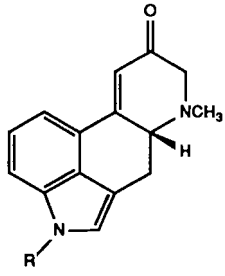
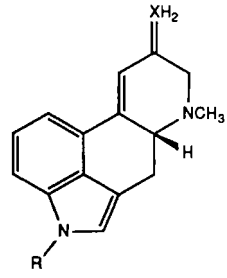


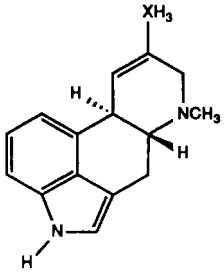
1; R = H
2; R = Ts

$Ph_3P=CH_2$/THF
-78°/ 24 hrs.



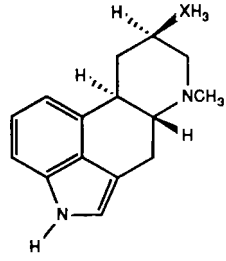
3 ; X = ^{12}C, R = H
4 ; X = ^{12}C, R = Ts
5 ; X = ^{14}C, R = Ts

$Li/NH_3/THF$



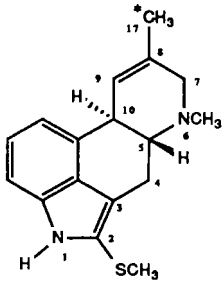
6; X = ^{12}C
8; X = ^{14}C

+



7 ; X = ^{12}C
9 ; X = ^{14}C

CH_3SCl/ CH_3SO_3H



10; LY 170542-^{14}C
• denotes radiolabel

To study the disposition and metabolism of LY 170542, radiolabeled material was required. Several possibilities exist for the location of the radiolabel in LY 170542. Material was prepared which contained the radiolabel in the 6-methyl group; radiorespirometry experiments showed that approximately 5 % of the dose was lost as $[^{14}C]$-CO_2. Similiar experiments with material radiolabeled in the 2-methylthio-moiety showed a 24 % loss of $[^{14}C]$-CO_2 in expired air.[6] To have radiolabeled material stable to loss of the label through metabolic demethylation, a synthesis of LY 170542 which was labeled in the C-8 methyl group was undertaken. Such a synthesis must maintain both absolute and relative stereochemistry in the final product. The plan was to synthesize17-$[^{14}C]$-agroclavine and convert it to 17-$[^{14}C]$-LY 170542 in the final step. Insertion of the label in an intermediate derived from lysergic acid and convertion to 17-$[^{14}C]$-agroclavine, while maintaining stereochemical control was considered feasible.[7]

RESULTS AND DISCUSSION

Ninomiya recently reported on the first total synthesis of ±-lysergene and ±-agroclavine.[8] In this paper, ±-N-(4'-methoxybenzenesulfonyl)- 2,3-dihydro- lysergene was prepared (in a manner similiar to that described earlier in the total synthesis of ±-lysergic acid[9]) and was then converted to ±-2,3-dihydroagroclavine (as well as the 10-epimer) by reduction with sodium/ammonia. Bernardi and co-workers have synthesized 9,10-didehydro-6-methylergolin-8-one (**1**) from lysergic acid via a five step sequence which maintains absolute stereochemistry.[10] We envisioned the synthesis of lysergene from **1** via a Wittig reaction as reported earlier in our preliminary communication.[7]

Reaction of methylenetriphenylphosphorane with **1** at -78°C in THF yielded lysergene (**3**); however, in only 12% yield. Conversion of **1** to the corresponding 1-(4'-toluenesulfonyl) derivative (**2**) by reaction with p-TsCl/K_2CO_3 was very erratic. Substitution of Cs_2CO_3 as the base allowed the smooth conversion of **1** to **2** in moderate yields (presumeably the result of the greater solubility of Cs_2CO_3). Reaction of **2** with methylenetriphenylphosphorane or the corresponding ^{14}C- labeled isotopomer (prepared from methyltriphenylphosphonium iodide by deprotonation with potassium t-butoxide) in THF at -78°C for 16- 24 hours provided, after quenching the reaction with dilute HCl, the hydrochloride salt of 1-(4'-toluenesulfonyl)-lysergene (**4**) or the analogous $[^{14}C]$- isotopomer (**5**).

While the lithium/ ammonia reduction of lysergene at -33°C yields a mixture of agroclavine (**6**) and festuclavine (**7**), reduction of the HCl salt of **4** (or its corresponding isotopomer **5**) in a like manner, yielded only **6** (or the analogous isotopomer **8**)[11]. A trace of 17-$[^{14}C]$-festuclavine (**9**) was evident by autoradiography in the radiolabeled reaction. In the above experiment, a substantial excess of lithium was used to assure complete reduction of **4** (or **5**).

Reaction of 17-$[^{14}C]$- agroclavine with methanesulfenyl chloride (prepared by the reaction of

dimethyldisulfide with sulfuryl chloride) in the presence of methanesulfonic acid yielded 17-[^{14}C]-LY 170542 (**10**) in an overall yield of 7.6%. The radiochemical purity was 98.8-99.2%; the specific activity was 48.07 μCi/mg (18.3 mCi/mmol).

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a Bruker WM-250 NMR spectrometer at 250 MHz (^{1}H) and 62.896 MHz (^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. ^{1}H and ^{13}C chemical shift assignments were made on the basis of two dimensional proton-correlated COSY and ^{1}H-^{13}C correlated NMR experiments.[12] Mass spectra were recorded on a Varian Associates MAT 731 mass spectrometer (field desorption) or a CEC 21-210 mass spectrometer (electron impact). Microanalytical data were determined in the Physical Chemistry Research Department of the Lilly Research Laboratories.

Radiochemical purity (RCP) was assessed by autoradiography employing E. Merck silica gel F-254 or aluminum oxide F-254 TLC plates and Kodak x-ray film BB-5. In addition RCP was determined using HPLC utilizing a Radiomatic Flo-One radiochemical detector.

Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl.

Flash chromatography was performed using the method described by Still et al. using E.M. Scientific silica gel 60 (230-400 mesh).[13]

Lysergene:

Methyltriphenylphosphonium bromide (0.447 g, 1.26 mmol) was suspended in THF (10 mL). n-BuLi (1.6 M, 1.11 mL) was added to the stirred mixture under argon at -10°C. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for an hour. The mixture was cooled to -78°C and **1**[10] (0.15 g, 0.63 mmol) was added; stirring at -78°C was continued for 20 hr. The mixture was allowed to warm to 0°C and filtered. Et_2O was added to the filtrate and the solution was washed with saturated brine, dried (anhydrous $MgSO_4$), and concentrated. The residue was crystallized from EtOAc to yield 0.018 g of lysergene (12 %). This material was identical in all respects to lysergene prepared from lysergol by reaction with Na/n-BuOH.[14] MS(FD) M^+ 236.

Lithium/Ammonia Reduction of Lysergene:

Lysergene (0.5 g, 2.12 mmol) was added to a mixture of THF (25 mL) and liquid ammonia (125 mL). Lithium wire (0.146 g, 21 mg-atom) was added in small chunks and the resulting blue solution was stirred at -33°C for 2 hr., whereupon the excess lithium was decomposed by the careful dropwise addition of saturated aqueous NH_4Cl.

The ammonia was allowed to evaporate and the remaining solution was diluted with Et_2O, washed with water, dried (anhydrous $MgSO_4$), and concentrated *in vacuo*. TLC of the crude reaction mixture (silica gel $CHCl_3$/EtOH/NH_4OH, 90:10:0.5) showed a mixture of agroclavine (r_f 0.72) and a closely related compound (r_f 0.66) . The crude mixture was purified by flash chromatography over silica gel, eluting in 10 mL fractions with $CHCl_3$/EtOH/NH_4OH 90:10:0.5. Fractions 9-11

contained agroclavine; fractions 15-17 contained material which proved to be festuclavine: mp 241-244°C (lit. 242-244°C [14]). NMR ($CDCl_3$): δ 1.01(d, 3H, 8-CH_3), 1.11(dd,J=12.1 Hz, 1H, 9-H, axial), 1.88 (dd, J=11.0 Hz, 1H, 7-H, axial), 2.01(m, 1H, 8-H), 2.11(m, 1H, 5-H), 2.46 (s, 3H, N-CH_3), 2.68(dd, J=12.1 Hz, 1H,9-H, equatorial), 2.68(dd, J=14.8 Hz,1H, 4-H, axial), 2.96(m, 2H, 7-H, equatorial, and 10-H), 3.41(dd, J=4.4 and 14.8 Hz, 1H, 4-H equatorial), 6.88(s, 1H, 2-H), 6.90(m, 1H, 12-H), 7.16 (d, 1H, 13-H), 7.17(d, 1H, 14-H), and 7.87(bs, 1H, N-H).

1-(4'-Toluenesulfonyl)-8,9-didehydro-6-methyl-ergolin-8-one,(2):

A mixture of **1**[10](5.0 g, 21 mmol), cesium carbonate (dried for 1 hr under vacuum at 80°C prior to use) (13.65 g, 42 mmol) in 250 mL of 2-butanone was stirred under argon for 10 min; then 4-toluenesulfonyl chloride (freshly recrystallized from hexane) (4.4 g, 23 mmol)was added. After stirring for 2 hrs, TLC (Al_2O_3, $CHCl_3$/hexane, 90:10) indicated that all of the starting material was consumed.

The mixture was filtered through Hi-Flo Supercel. The filtrate was evaporated *in vacuo* and the residue was redissolved in EtOAc. The EtOAc solution was washed twice with water, dried (anhydrous $MgSO_4$), and evaporated to yield **2**. The residue was flash chromatographed over silica gel (eluted in 50 mL fractions with $CHCl_3$/MeOH 97:3). Fractions 11-20 were concentrated and the residue crystallized from EtOH to yield **2** (2.35 g, 29%) as a crystalline solid, mp 140-143°C (with decomposition): UV(MeOH), λ_M(ε_M) 320 (12000), 261 (19890), 232 (16650) nm; MS(FD), M^+ 392; MS(EI), M^+392, 238, 209, 91 (base); ^{1}H-NMR ($CDCl_3$) δ 2.34 (s, 3H, 4'-CH_3), 2.55 (s, 3H, N-CH_3), 2.73 (dd, 1H, 4-H, axial), 3.14 (dd, 1H, 7-H, equatorial), 3.38 (m, 1H, 5-H), 3.47 (dd, 1H, 7-H, axial), 3.52 (dd, 1H, 4-H, axial), 6.72 (s, 1H, 9-H), 7.23 and 7.77 (q_{AB}, 4H, 3',5' and 2',6'-H), 7.37 (m, 1H, 13-H), 7.46 (d, 1H, 12-H), and 7.93 (d, 1H, 14-H); ^{13}C-NMR ($CDCl_3$) 21.39 (C-4' CH_3), 25.75 (C-4), 42.00 (N-CH_3), 61.18 (C-5), 63.09 (C-7), 115.63 (C-14), 116.23 (C-3), 118.58 (C-12), 120.72 (C-9), 121.29 (C-2), 126.64 (C-2' and C-6'), 129.84 (C-3' and C-5'), 135.28 (C-1'), 145.02 (C-4'), and 194.95 (C-8).

Anal Calcd for $C_{22}H_{20}N_2O_3S$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.09; H, 4.92; N, 7.27.

1-(4'-Toluenesulfonyl)-lysergene, Hydrochloride (4):

A mixture of methyltriphenylphosphonium iodide (0.927 g, 2.30 mmol) and potassium *tert.*-butoxide (0.257 g, 2.30 mmol) was stored under argon and diluted with THF (10 mL, the mixture immediately turned yellow). After stirring at room temperature for 0.5 hr, the mixture was cooled to -78°C whereupon **2** (0.3 g, 0.765 mmol) was added. Stirring was continued at -78°C for16 hr, then slowly allowed to warm to 10°C and diluted with Et_2O. The resulting mixture was

filtered and acidified with dilute HCl; a white solid formed which was collected by filtration and dried to yield **4** (64 %); TLC: silica gel, $CHCl_3$/MeOH, 90:10, r_f 0.88; Al_2O_3, $CHCl_3$/hexane, 90:10, r_f 0.69; UV (MeOH) $\lambda_M(\varepsilon_M)$238 (23367), 311 (24402); MS(FD) M^+390; MS(EI) M^+390, 235, 124, 91(base); ^{1}H-NMR ($CDCl_3$) (as free base) δ 2.31 (s, 3H, 4'-CH_3), 2.51 (s, 3H, N-CH_3), 2.60 (m, 1H, 4-H, equatorial), 3.15 (m, 2H, 5-H and 7-H, equatorial), 3.40 (m, 1H, 4-H, equatorial), 3.45 (m, 1H, 7-H, axial), 4.97 and 5.06 (s, 2H, 8-CH_2), 6.89 (s, 1H, 9-H), 7.19 and 7.76 (q_{AB}, 4H, 3',5'-H and 2',6'-H), 7.22 (s, 1H, 2-H), 7.31 (m, 1H, 13-H), 7.33 (m, 1H, 12-H), and 7.78 (m, 1H, 14-H); ^{13}C-NMR ($CDCl_3$) (as free base) 21.42 (4'-CH_3), 26.68 (C-4), 42.72 (N-CH_3), 58.36 (C-7), 61.47 (C-5), 111.93 (C-8 CH_2), 112.70 (C-14), 116.58 (C-12), 119.99 (C-2), 122.93 (C-9), 125.81 (C-13), 126.70 (C-2' and C-6'), 129.75 (C-3' and C-5').

Anal Calcd for $C_{23}H_{22}N_2O_2S$·HCl (1.5 H_2O): C, 60.85; H, 5.77; N, 6.17. Found: C, 61.17; H, 5.37; N, 5.84.

17-[^{14}C]-1-(4'-Toluenesulfonyl)-lysergene, Hydrochloride (5):

A mixture of potassium *tert*-butoxide (0.857 g, 7.65 mmol) and [^{14}C]-methyltriphenyl-phosphonium iodide (Pathfinder Laboratories, sp act 20.5 mCi/mmol) (2.97 g, 7.34 mmol, 150.47 mCi) was diluted with THF (15 mL) under argon. After stirring for 1 hr at room temperature, the mixture was cooled to -78°C and **2** (0.977 g, 2.49 mmol) was added. Stirring at -78°C was continued for 16 hrs and the mixture was then allowed to warm to 10°C.

The mixture was diluted with Et_2O and filtered. The filtrate was acidified with 8 mL of 1N HCl and a gummy solid formed. The Et_2O/THF was decanted and the residue was triturated with fresh Et_2O. Water was added and the crystalline solid was collected by filtration and dried. The white solid (**5**, 0.493g, 46.5 %) was identical to **4** by TLC on silica gel ($CHCl_3$/MeOH90:10) and Al_2O_3 ($CHCl_3$/hexane 90:10) and autoradiography showed only one radioactive component.

Lithium/Ammonia Reduction of 1-(4'-Toluenesulfonyl)-lysergene Hydrochloride (4):

A THF solution (10 mL) of **4** (0.040 g, 0.094 mmol) was added to 50 mL of anhydrous ammonia (at -33°C). The mixture was stirred and lithium metal (0.040 g, 5.8 mg-atom) was added slowly in small pieces (at first the blue color dissipated rapidly, then the solution remained blue). Stirring was continued for 2 hrs; the excess lithium was decomposed by the careful dropwise addition of saturated aqueous NH_4Cl.

Et_2O was added after the ammonia evaporated and the resulting solution was washed twice with water, dried (anhydrous $MgSO_4$), and concentrated *in vacuo*. The residue was purified by TLC on five 5x20 mm analytical Al_2O_3 plates ($CHCl_3$/hexane 90:10) to yield agroclavine (**6**); 0.024 g (91%), which was identical to authentic agroclavine by TLC, NMR, and MS. $[\alpha]_D$= -181.8° (pyridine); literature: $[\alpha]_D$= -182°(pyridine).[15]

Lithium/Ammonia Reduction of 17-[^{14}C]-1-(4'-Toluenesulfonyl)-lysergene, Hydrochloride (5):

A THF (40 mL) suspension of **5** (0.493 g, 1.16 mmol) was added to 250 mL of anhydrous ammonia at -33°C. Lithium metal (0.493 g, 71.4 mg-atom) was added in small pieces as described above. After work-up, autoradiography of the crude product showed only a trace of 17-[^{14}C]-festuclavine. The mixture was purified by chromatography over Activity III Al_2O_3, by elution in 20 mL fractions with $CHCl_3$/hexane 90:10. Fractions 2-10 were combined and the residue after evaporation was re-chromatographed on seven 20x20 mm analytical silica gel TLC plates. The plates were developed with $CHCl_3$/EtOH 90:10. The zones containing 17-[^{14}C]-agroclavine (**8**) were scraped and eluted with $CHCl_3$/EtOH 90:10 to yield 0.143 g (52 %) of **8** which was identical to authentic agroclavine by TLC.

17-[^{14}C]-8,9-Didehydro-6,8-dimethyl-2-methylthioergoline Mesylate (LY 170542), 10:

Methanesulfenyl chloride was prepared *in situ* by the reaction of an ice-cold solution of dimethyldisulfide (0.030 g, 0.317 mmol) in methylene chloride (2 mL) with sulfuryl chloride (0.045 g, 0.33 mmol). The resulting solution was stirred at 0°C for 0.5 hrs and then added to **8** (0.144 g, 0.61 mmol) and methanesulfonic acid (0.058 g, 0.61 mmol) in 5 mL of methylene chloride at 0°C under argon. After stirring for 0.5 hrs, the mixture was made basic with conc. NH_4OH. The aqueous layer was extracted three times with 10 mL of methylene chloride. The combined methylene chloride extracts were washed twice with water, dried (anhydrous $MgSO_4$), and concentrated.

The residual oil was redissolved in 0.4 mL of absolute EtOH and treated with methanesulfonic acid (0.058 g, 0.605 mmol) and 0.5 mL of EtOH. The mixture was stirred at 0°C until crystallization occurred. The mixture was filtered and the crystalline product was purified by preparative TLC on silica gel ($CHCl_3$/EtOH 80:20). Reconversion to the mesylate salt and crystallization yielded 0.052 g of **10** (23 %) as a white crystalline salt (sp act 48.1 μCi/mg or 18.3 mCi/mmol). This material was shown to be identical to authentic LY 170542[3] by HPLC (DuPont Zorbax ODS; MeOH/MeCN/0.1 M NH_4OAc 40:40:20 at 2 mL/min, UV at 289 nm, radiochemical detector) and

TLC: Al_2O_3, $CHCl_3$/hexane 80:20, r_f 0.39; silica gel, CH_2Cl_2/MeOH/NH_4OH 90:10:0.5, r_f 0.63 with radiochemical purity of 99 and 98.8 % respectively.

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