The Synthesis of 8-ß-[(Methylsulfinyl-[^{18}O])-methyl]-6-propylergoline

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SUMMARY

The synthesis of ^{18}O-labeled 8-ß-[(methylsulfinyl)-methyl]-6-propyl-ergoline (pergolide-[^{18}O]-sulfoxide) of undetermined stereochemistry by the reaction of 8-ß-(methylthiomethyl)-6-propyl-ergoline (pergolide) with *bis*-(4-methoxyphenyl)-selen-[^{18}O]-oxide in acetic acid is described. Although the yields were low and the incorporation of ^{18}O was not high, this procedure represents a convenient method for the preparation of ^{18}O-labeled sulfoxides of pergolide and other sulfides present in compounds for which the usual methods are inappropriate.

Key Words: oxygen-18, pergolide, diarylselenoxide, sulfoxides

INTRODUCTION

Pergolide mesylate (LY 127809) is a dopamine agonist currently undergoing clinical evaluation for the treatment of parkinsonism.[1] Parli *et al* have reported that the major identified metabolite of pergolide is the corresponding sulfoxide .[2] Since several sulfide and sulfoxide-containing drugs are known to undergo reversible metabolic oxidation-reduction reactions,[3,4,5] there was interest in determining if the sulfoxide is an end product of metabolism or whether once formed it is reduced back to pergolide. By undertaking pharmacokinetic experiments utilizing ^{18}O-labeled drugs and GC-MS

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techniques Murphy and Sullivan[6] and Eichelbaum *et al*[7] have studied the kinetics and reversibility of similiar metabolically-mediated sulfur redox chemistry.

DISCUSSION AND RESULTS

Although several methods for the preparation of sulfoxides from the corresponding sulfide are known, the most common method for the preparation of ^{18}O-sulfoxides involves the bromination of the sulfide with bromine or N-bromosuccinimide followed by hydrolysis of the resulting bromosulfonium salt with ^{18}O-water in the presence of potassium carbonate.[8] Attempts to oxidize pergolide under similiar conditions resulted in bromination of the indole ring in the 2-position.[9]

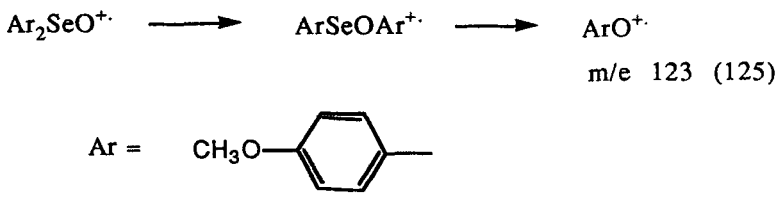
Recently Ogura *et al* described the use of *bis*-(4-methoxyphenyl)selenoxide as a mild and selective oxidizing agent which undergoes disproportionation with sulfides in the presence of acetic acid forming the corresponding sulfoxide and *bis*-(4-methoxyphenyl)selenide.[10] *Bis*-(4-methoxyphenyl)selenoxide is conveniently prepared from the dibromoselenide by reaction with sodium hydroxide, thus substitution of ^{18}O-water afforded the requisite *bis*-(4-methoxyphenyl)selen-[^{18}O]-oxide which was highly enriched in ^{18}O (93 %) (Scheme 1).

SCHEME 1

$$Ar_2SeBr_2 + Na^{18}OH \xrightarrow{H_2{}^{18}O} Ar_2Se^{18}O$$

The incorporation of ^{18}O was determined by mass spectrometry. Although the molecular ion in the EI-mass spectrum was absent, the base peak which corresponds to the ion derived from rearrangement of the molecular ion to a selenenic acid ester ion followed by cleavage of the resulting SeO bond was present (Scheme 2).[11]

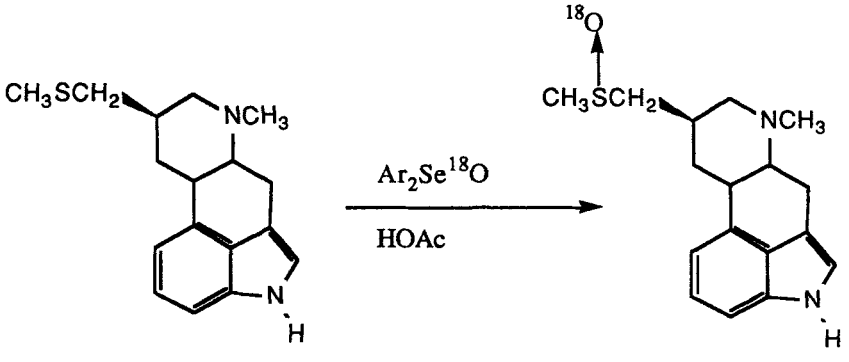
SCHEME 2



Ogura *et al* reported high yields in the clean conversion of sulfides to sulfoxides;[10] however, the oxidation of pergolide with *bis*-(4-methoxyphenyl)selenoxide was not quite as straightforward, although pergolide sulfoxide was isolated in low yield.

Reaction of pergolide with ^{18}O-*bis*-(4-methoxyphenyl)selenoxide yielded 8-ß-8-[(methylsulfinyl-[^{18}O]-methyl)]-6-propylergoline (pergolide-[^{18}O]-sulfoxide) which was purified by flash chromatography

SCHEME 3



over silica gel (Scheme 3). The ^{18}O-incorporation in the pergolide-[^{18}O]-sulfoxide was determined by FAB-MS. In the initial experiments, the incorporation was low (49%) which was initially presumed to be due to incomplete conversion of pergolide to the labeled sulfoxide and subsequent air oxidation to the non-labeled sulfoxide. In later experiments, an excess of ^{18}O-selenoxide was used to ensure complete

conversion to pergolide-[^{18}O]-sulfoxide; however, the incorporation was still only 53%. A more likely explanation for the low incorporation is that an exchange reaction occurs between the ^{18}O-selenoxide and the solvent acetic acid. Oae *et al* have reported similiar exchange between optically active ^{18}O-sulfoxides and acetic acid at 130°.[12]

Perhaps such exchange reactions could be eliminated or minimized by a more prudent choice of proton source or use of only catalytic quantities of acetic acid, thus allowing higher incorporations. Hu *et al* recently described the use of polymer supported diarylselenoxides as useful oxidizing agents.[13] These reagents have the advantage of allowing one to simply filter away the diarylselenide or any unreacted selenoxide from the reaction mixture which should facilitate isolation of the product.

The material described in this paper will be used in a study of the biological oxidation-reduction reactions of pergolide and its sulfoxide.

EXPERIMENTAL

Methods:

Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. Mass spectra were recorded from the following mass spectrometers: FAB, VG Corporation, Ltd., ZAB-3F; EI, CEC 21-210; and FD, Varian Corp., MAT 731.

Flash chromatography was performed on 230-400 mesh silica gel from EM Scientific according to the method described by Still *et al.* [14]

Sodium-[^{18}O]-hydroxide and [^{18}O]-water were purchased from E. Merck and KOR Isotopes.

Syntheses:

Bis-(4-methoxyphenyl)-selen-[^{18}O]-oxide:

Bis-(4-methoxyphenyl)-selenide dibromide[15](0.679 g, 1.5 mmol) was added to sodium [^{18}O]-hydroxide (97% enriched, 1 g , 3 M), whereupon the mixture immediately became tacky (color changed from orange to white) and finally solidified after 30 min. The mixture was allowed to stand at room temperature for 1 hour and then was thoroughly triturated with methylene chloride (the solution changed from yellow to water white as the last remaining dibromoselenide was consumed). The methylene chloride solution (top layer) was separated and dried (anh. $MgSO_4$), then concentrated to a white solid: mp 135-6^{o}C (lit. 142^{o}C [16]); 0.403 g, 83.6%;

M^+(FD-MS) 312; ^{18}O-incorporation by EI-MS, 96%.

8-ß-[(Methylsulfinyl-[^{18}O])-methyl]-6-propylergoline:

An acetic acid (25 mL) solution of 8-ß-methylthiomethyl-6-propyl-ergoline (0.368 g, 1.17 mmol) was treated with a slight excess of *bis*-(4-methoxyphenyl)-selen-[^{18}O]-oxide (0.402 g, 1.29 mmol) and the resulting mixture was stirred under argon in the dark for 16 hours at which time all of the ^{18}O-selenoxide was consumed (tlc on silica gel $CHCl_3$/acetone/MeOH/NH_4OH 63:27:7:2). The acetic acid was removed *in vacuo* . The residue was redissolved in methylene chloride and extracted with 0.75 mL of 1N HCl and the organic layer was rewashed with water. The combined aqueous extracts were layered with methylene chloride and made basic with 0.75 mL of 2 N NaOH. The aqueous layer was extracted with 3X5 mL of methylene chloride; the combined methylene chloride extracts were dried (anhydrous $MgSO_4$) and concentrated *in vacuo*.

The residue was purified by flash chromatography over silica gel.

The product was eluted with EtOAc/MeOH/NH_4OH (75:25:1) collecting 10 mL fractions. The product was contained in fractions 11-13 which were combined and concentrated *in vacuo*. The residue was triturated with EtOAc and collected by filtration. The amorphous solid was washed with pentane and dried to yield 8-ß-[(methylsulfinyl-[^{18}O])-methyl]-6-propylergoline; mp 150-153^{o}C(dec.)(0.0387 g, 10%). FAB-MS indicated 52.6% ^{18}O-incorporation.

This material was identical to 8-ß-(methylsulfinylmethyl)-6-propyl-ergoline (which was prepared from 8-ß-(methylthiomethyl)-6-propylergoline by reaction with 3-chloroperbenzoic acid in 1:1 EtOH/ 0.01 N HCl[17]) by TLC (silica gel, $CHCl_3$/MeOH/HOAc 13:6:1 and $CHCl_3$/MeOH/acetone/NH_4OH 63:7:27:2) and HPLC (Altech C-18, 65% MeCN:35% 0.01 M ammonium formate, 1 mL/min. UV at 290 nm).

Anal. Mol wt calcd for $C_{19}H_{26}N_2{}^{18}OS$: 333.1887 (FAB-MS, $M^+ + H$). Found: 333.1901

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