THE SYNTHESIS OF ^{14}C-LABELED SUICIDE INACTIVATORS OF MONOAMINE OXIDASE*

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SUMMARY

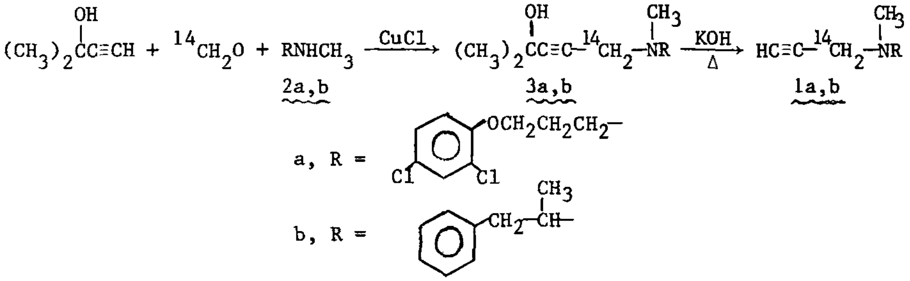
N-[3-(2,4-dichlorophenoxy)propyl]-N-methyl-2-propynylamine-1-^{14}C (^{14}C-clorgyline, 1a) and L-N,α-dimethyl-N-2-propynyl-1-^{14}C-phenethylamine (^{14}C-L deprenyl, 1b) were synthesized by the Mannich reaction of 2-methyl-3-butyn-2-ol, ^{14}C-formaldehyde, and secondary amines 3-(2,4-dichlorophenoxy)-N-methylpropylamine (2a) or L-N,α-dimethylphenethylamine (2b) followed by KOH catalyzed elimination of acetone from the respective Mannich base 3a or 3b.

Key Words: ^{14}C-clorgyline, ^{14}C-deprenyl, ^{14}C-suicide enzyme inactivators

INTRODUCTION

In our studies of the metabolism of suicide inactivators (1) of the isozymes of monoamine oxidase (MAO) type A and B we required a synthetic sequence which could be used to label the methylene carbon of substituted propargylamines clorgyline (1a) and L-deprenyl (1b) with isotopic carbon. We have found that the Mannich reaction using 2-methyl-3-butyn-2-ol as an acetylene precursor with formaldehyde and the appropriate secondary amine followed by KOH catalyzed elimination of acetone from the Mannich base provided a convenient synthetic route to propargylamines (2).

We report here the use of ^{14}C-formaldehyde in this sequence to produce ^{14}C-labeled clorgyline (1a) and L-deprenyl (1b) in radiochemical yields of 33 and 28% respectively.



$$(CH_3)_2\overset{OH}{\overset{|}{C}}C{\equiv}CH + {}^{14}CH_2O + \underset{2a,b}{RNHCH_3} \xrightarrow{CuCl} \underset{3a,b}{(CH_3)_2\overset{OH}{\overset{|}{C}}C{\equiv}C{-}{}^{14}CH_2{-}\overset{CH_3}{\overset{|}{N}}R} \xrightarrow[\Delta]{KOH} \underset{1a,b}{HC{\equiv}C{-}{}^{14}CH_2{-}\overset{CH_3}{\overset{|}{N}}R}$$

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EXPERIMENTAL

Radioactivity determination was carried out with a Beckman Model LS200 liquid scintillation spectrometer. Efficiency corrections were made using ^{14}C-toluene, an internal standard.

N-[3-(2,4-Dichlorophenoxy)propyl]-N-methyl-2-propynlamine-1-^{14}C (^{14}C-1a)·HCl. To 0.24 g (0.089 mmol) of 2a·HCl (3) in 0.25 ml of H_2O was added a mixture of 0.15 ml of ^{14}C-formaldehyde (2.22 x 10^9 dpm (4), 44 mCi/mmol, New England Nuclear) and 5.4 µl (0.066 mmol) of 37% aqueous formaldehyde in 0.3 ml of H_2O. This was heated briefly to dissolve the amine salt and 4 mg of CuCl was added. The pH was adjusted to 8 with 0.1 ml of 7.5% $NaHCO_3$ and 8.6 µl (0.089 mmol) of 2-methyl-3-butyn-2-ol in 0.3 ml of dioxane was added. The mixture was heated (110°) with stirring in a sealed tube for 3 hrs, allowed to cool to 25° and 0.3 ml of NH_4OH (con) added. The mixture was extracted with ether, the extracts dried (K_2CO_3) and the solvent removed to yield 1.26 x 10^9 dpm of 3a as a pale yellow oil.

To a film of KOH (0.2 ml of 1 M KOH, lyophilized on the bottom and sides of a test tube with a vacuum adapter and heated under vacuum for 2 min at 150°) was added an ethereal solution of 3a. This was evaporated to dryness using a stream of N_2, a cold finger attached and the residue heated under vacuum (1 mm) at 150° for 1 min. The material adhering to the cold finger was dissolved in ether:hexane (1:1) and passed over a 4 x 0.5 cm silica gel column and eluted with ∿ 3 ml of the same solvent. The solvent was removed, the residue dissolved in ether, treated with dry HCl and recrystallized (CH_3OH:ether) to yield 0.49 x 10^9 dpm of ^{14}C-1a (radiochemical yield = 33%) having a specific activity of 5.6 mCi/mmol. The product was dissolved in water and passed through a millipore filter (0.22 µ) and stored in the cold in solution. Radiochemical purity was determined to be > 98% by thin layer chromatography on silica gel in 2 solvents: n-BuOH:HOAc:H_2O (4:1:5), R_f = 0.6 and $CHCl_3$:EtOH:H_2O (8:3:5), R_f = 0.95.

N,α-Dimethyl-N-2-propynyl-1-^{14}C-phenethylamine·HCl (^{14}C-1b). To 0.0165 g (0.089 mmol) or 2b·HCl (2) in 0.1 ml of H_2O was added 4 mg of CuCl and a mixture of ^{14}C-formaldehyde (2.22×10^9 dpm (4), 44 mCi/mmol, New England Nuclear) and 5.4 µl (0.066 mmol) of 37% aqueous formaldehyde in 0.3 ml of H_2O. This was heated briefly, the pH adjusted to 8 with 0.1 ml of 7.5% $NaHCO_3$, and 8.6 µl (0.089 mmol) of 2-methyl-3-butyn-2-ol in 0.3 ml of dioxane added. The mixture was heated with stirring in a sealed tube at 110° for 8 hrs and allowed to cool to 25°. Ammonium hydroxide (con) (0.3 ml) was added and the reaction mixture worked up as previously described to give 1.01×10^9 dpm of an oil which was pyrolyzed and worked up as described for ^{14}C-**1a** to give 0.41×10^9 dpm (radiochemical yield 28%) of an oil which was dissolved in ether and treated with dry HCl. The product was dissolved in water and passed through a millipore filter (0.22 µ) and stored in the cold in solution. Tlc of the free base on silica gel in ether:hexane (1:1) ($R_f = 0.65$) and benzene:CCl_4 (1:1) ($R_f = 0.35$) showed that the product was radiochemically pure. The specific activity was 4.3 mCi/mmol.

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4. Assay of this [^{14}C]-formaldehyde by forming a derivative with 5,5-dimethyl-1,3-cyclohexanedione showed that 62-67% of the radioactivity was in the chemical form of formaldehyde.