SYNTHESIS OF 1-4' -ETHYLPHENOXY- ^{14}C (U)-6,7-EPOXY- 3,7 - DIMETHYL- 2 -OCTENE. A JUVENILE HORMONE ANALOG.

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SUMMARY

The preparation of 1-4' ethylphenoxy-^{14}C(U)-6,7- epoxy - 3,7-dimethyl-2-octene[1,2] involved a single reaction wherein 4-ethylphenol-^{14}C(U)[3] was mixed with 1-chloro-6,7-epoxy-3,7 -dimethyl-2-octene in an acetone water solution at reflux using potassium carbonate as a hydrogen chloride acceptor. Althoug this juvenile hormone analog (JHA) normally shows good shelf stability, the quality of the labeled material which had been purified by Column Chromatography deteriorated significantly when stored neat for a period of 17 days.

INTRODUCTION

The synthesis of 1-4'-ethylphenoxy-^{14}C(U)-6,7-epoxy-3,7-dimethyl-2-octene, a candidate JHA of Stauffer Chemical Company, was undertaken to supply radio labeled material for metabolism, tissue residue and chemical stability studies.

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Anhydrous potassium carbonate, 195 mg (1.41 mM), was charged to a reactor containing 72 mg (0.6 mM) of 4-ethylphenol-^{14}C(U) having a specific activity of 17 mCi/mM. This mixture was diluted with 2 ml of an acetone/water 97/3 stock solution which contained 290 mg of potassium iodide per 100 ml of solution. The reaction was initiated by the addition of 1-chloro-6,7-epoxy-3,7-dimethyl-2-octene, 130 mg (0.69 mM), and subsequent heating of the mixture to reflux. The reaction scheme is illustrated in Figure 1.

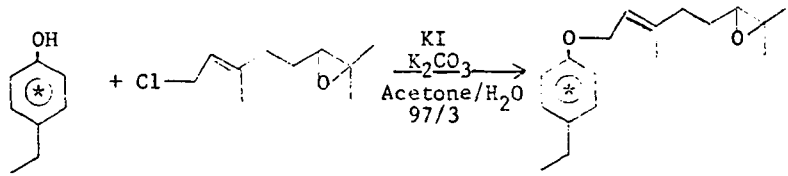

Figure 1

The course of the reaction was monitored at six hour intervals by gas chromatographic analysis. At the end of each six hour reflux period, a 1 λ aliquot was withdrawn from the reaction mixture, charged to a 2 ml vial where the acetone was allowed to evaporate, and the residue was dissolved in 20 λ of carbon disulfide. A 1 λ portion of this sample was injected into a Varian Aerograph-204-1B gas chromatograph which was fitted with a 6' x 1/4" Pyrex column packed with 5% Carbowax 20M on 80/100 mesh Gas Chrom Q (silylated diatomaceous earth), a hydrogen flame ionization detector, and a Cary ion chamber with vibrating reed electrometer. The injection temperature was 220°C, the

column temperature was held at 200°C until the JHA was eluted, then programed to 250°C at 20°C/min. The hydrogen flame ionization detector, the effluent splitter and the transfer line were held at 275°C. The ion chamber had a volume of 275 ml and was held at 290°C. Argon was used as a carrier gas and an ion chamber purge gas.

Gas phase liquid radiochromatographic (GLRC) analysis indicated that the reaction mixture attained 96% completion after 24 hours of reflux. The reaction mixture was diluted with 2 ml of acetone and filtered to remove the potassium chloride. The reactor, filter and filter cake were thoroughly washed with acetone. The combined filtrate and washes were stripped of solvent. The residue was dissolved in n-pentane and this solution washed with 0.5 ml of 5% aqueous sodium hydroxide to remove unreacted 4-ethylphenol. The pentane solution was washed with four portions of 0.5 ml of water, dried over anhydrous magnesium sulfate, filtered and stripped of solvent to determine the crude yield. The crude product had a radiochemical purity of 92% as determined by GLRC.

The crude JHA was dissolved in 0.5 ml of n-pentane and charged to a 24" x 1/2" Pyrex column, which had been dry packed with 12.5 g of Merck Silica Gel H. The reactor was washed with three 0.5 ml portions of n-pentane which were charged to the column. The product was eluted from the column with pentane/diethyl ether, 80/20 (v/v) in 34 fractions, each collected over a period of three minutes. A 1 λ sample of each fraction was spotted on a tlc plate and cochromatographed with a reference standard using the same solvent system indicated above. Those fractions which were

shown to contain the JHA were assayed by GLRC to quantitatively determine the radiochemical purity. Those fractions having radiochemical purities higher than 95% were combined and stripped to a residue to yield 105 mg of product (64.5% of theoretical).

The material was stored neat for 17 days. Analysis by GLRC showed the formation of higher boiling impurities indicating radiolytically induced polymerization, since the non-radioactive JHA has good shelf stability. The product was purified in small portions by preparative tlc (benzene/diethyl ether 20/1 v/v). All radioactive bands were collected from the tlc plate and assayed individually by liquid scintillation counting. This procedure indicated that only 85% of the radioactivity applied to the chromatoplate was the JHA. The purified material was stored at 5°C in a dilute hexane solution over potassium carbonate and has shown relatively high stability.

(1) Pallos, F.M., Menn, J.J., Letchworth, P.E., and Mlaullis, J.B., Nature (London) 232, 486 (1971).

(2) Pallos, F.M., Lee, H., and Menn, J.J. - Belgian Patent 734,904.

(3) Purchased from New England Nuclear Corp., Boston, Massachusetts.