

THE SYNTHESIS OF ^{14}C -EUGENOL AND ISOEUGENOL LABELED IN THE METHOXY POSITION

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SUMMARY

Methylation under pressure of o-allyloxyphenol with ^{14}C -methyl iodide was successfully used for the synthesis of ^{14}C -eugenol and isoeugenol labeled in the methoxy position. Eugenol and isoeugenol are important compounds in the practice of dentistry.

INTRODUCTION.

Eugenol and its isomerization product isoeugenol have been used by themselves or in combinations with metal oxides in almost all phases of dentistry^(1, 2, 3). Little useful information exists on the mode of action, distribution, metabolism, etc. of these compounds^(4, 5). To facilitate these studies it became necessary to develop a method for the synthesis of ^{14}C -eugenol and isoeugenol.

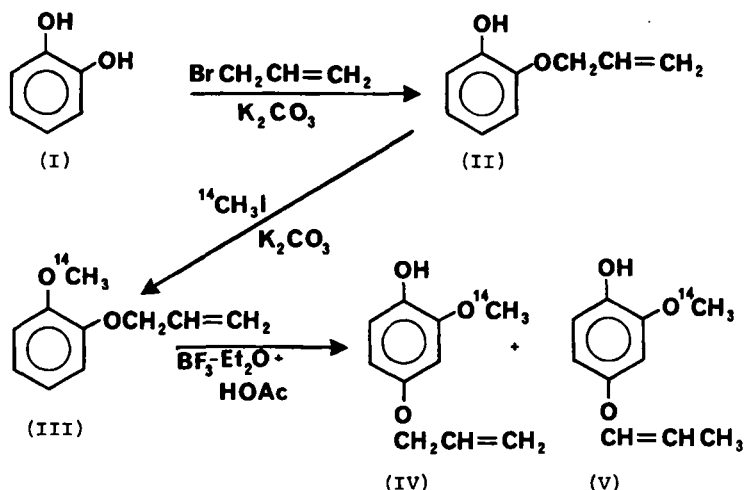
DISCUSSION.

Starting with catechol (I), as shown in Scheme I, o-allyloxyphenol (II) was obtained in a 44% yield by treatment with allyl bromide and sodium carbonate⁽⁶⁾. This intermediate was made on a large scale and purified by

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SCHEME I

vacuum distillation. Labeling was introduced at the next step when (II) was heated in a sealed ampoule with ^{14}C -methyl iodide, sodium carbonate, and acetone^(7, 8). The product ^{14}C -o-allyloxycatechol (III) was isolated by extraction with chloroform. Compound (III) was used in the final step without further purification. The labeled runs utilized 1-2 mmoles of ^{14}C -methyl iodide with total activities ranging from 4 to 10 mCi's. The product was characterized using thin layer chromatography (TLC) and compared to an authentic sample prepared by the method of von Auwers⁽⁷⁾. The final step in the syntheses involved the rearrangement of the labeled (III) compound to eugenol (IV) and isoeugenol (V) by using boron trifluoride etherate and glacial acetic acid catalyst⁽⁹⁾. This rearrangement was carried out by heating in a stoppered test tube at 73-78°C for 45 minutes (higher temperatures lead to extensive polymerization). The product was worked up by extractions with chloroform and sodium hydroxide, acidification and re-extraction into chloroform. The base

washed chloroform extract yielded some 45% unreacted starting material (III) which could be re-cycled in subsequent runs. Purification was effected by preparative scale gas chromatography. The yields of labeled eugenol and isoeugenol based on initial ¹⁴C-methyl iodide were 16% and 5% respectively. In addition smaller amounts of guaiacol, 6-allyleugenol and other non-identified compounds were obtained.

EXPERIMENTAL.

o-allyloxyphenol. A 250 ml flask fitted with stirrer, reflux condenser and drying tube was charged with 40 g (0.33 mole) of allyl bromide, 36.2 g (0.33 mole) catechol, and 75 ml of acetone. Anhydrous sodium carbonate (45 g; 0.45 mole) was added slowly while the mixture was being stirred. The combined reactants were refluxed overnight. The excess carbonate was then filtered off and the solvent removed. To the residual oil 25 ml of chloroform and 2 ml of dilute sulfuric acid was added. The chloroform solution was first washed with water and then with 5% sodium hydroxide until the final extract gave no turbidity with acid. The combined extracts were acidified with dilute acid and re-extracted with chloroform. The chloroform solution was water washed, dried over magnesium sulfate and vacuum distilled. The product, b.p. 125-130°C/35 mm weighed 22 g (44% yield).

¹⁴C-methoxy o-allyloxyanisole. ¹⁴C-methyl iodide, 373 mg (2.63 mmole, 4 mCi) was distilled into a large ampoule cooled at -5°C. The ampoule was then charged with 395 mg (2.63 mmole) of o-allyloxyphenol and 320 mg (0.32 mmole) of freshly ignited sodium carbonate and sufficient dry acetone to bring the total volume up to 5 ml. The ampoule was sealed and heated at 100°C for 30 hours. The ampoule was cooled and the contents poured into 5 ml of water. The mixture was extracted with two, 5 ml portions of chloroform. The chloroform extracts were washed with four, 3 ml portions each of dilute sodium hydroxide and then washed with water. The base washed chloroform layer was dried and solvent stripped under nitrogen. The residual oil gave only one spot on a

TLC plate with the same R_f value as an authentic sample. The yield was approximately 45%. Identification of the product on "cold" runs was also confirmed by infrared comparison and TLC.

^{14}C -methoxy eugenol and isoegenol. A 10 cm test tube was charged with ^{14}C -methoxy-o-allyloxyanisole prepared in the previous step. To this was added 2 drops of 5% boron trifluoride etherate and 5 drops of glacial acetic acid. The stoppered mixture was swirled and heated at 73-78°C for 45 minutes^(7, 8). To the cooled mixture was added 2 ml of water and 2 ml of chloroform. After shaking the aqueous phase was removed and extracted with two, 3 ml portions of chloroform. This was combined with the chloroform layer and extracted with two, 3 ml portions each of 5% sodium hydroxide. The combined alkaline extracts were acidified with a minimum of concentrated hydrochloric acid and re-extracted three times each, with 2 ml of chloroform. The combined extracts were dried over magnesium sulfate and concentrated to a small volume. The mixture was then fractionated by preparative scale gas chromatography using a Nester-Faust, 850 prepchromatic instrument. The yield of ^{14}C -eugenol in this step was 35% with an overall yield based on ^{14}C -methyl iodide of 16%. The yield of ^{14}C -isoeugenol was 10%.

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