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Synthesis of Geraniol-7-^{14}C

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SUMMARY

Geraniol-7-^{14}C has been synthesized in an overall yield of 46 %, starting with acetone-2-^{14}C.

INTRODUCTION.

It has been suggested by Erdtman [1] that β-thujaplicin (9), and isomeric isopropyltropolones found in the heartwood of *Thuja* species, are modified monoterpenes. Their biosynthesis could plausibly involve a ring enlargement of a cyclohexano-terpene (8), which would be derived from geraniol (7). We desired to test this hypothesis by the administration of labelled geraniol to *Thuja plicata* (Western Red Cedar). Geraniol-2-^{14}C [2, 3, 4] and -3-^{14}C [5] have been previously described, however these isotopically labelled geraniols would be expected to yield thujaplicins labelled in the tropolone ring at positions difficult to isolate by a systematic degradation. Geraniol-7-^{14}C would be a more desirable precursor since it should yield β-thujaplicin labelled on the central carbon atom of its isopropyl group, if it is indeed a modified monoterpene. The present paper describes the synthesis of geraniol-7-^{14}C from commercially available acetone-2-^{14}C.

Reaction of acetone with vinyl magnesium bromide yielded 2-methyl-3-buten-2-ol (1). This allylic alcohol on treatment with phosphorus tribromide afforded 3,3-dimethylallyl bromide [6], which was used to alkylate ethyl acetoacetate [7]. Hydrolysis of the resultant β-keto ester (6) yielded 6-methyl-5-hepten-2-one (5), which was purified by chromatography on alumina. Reaction of this ketone with the sodium salt of triethylphosphonoacetate yielded a mixture of *cis* (20 %) and *trans* (80 %) ethyl 3,7-dimethyl-2,6-octadienoate (4 and 3 respectively), which were separated by preparative thin layer chromatography on silica gel. Reduction of the *trans*-isomer with lithium aluminum hydride yielded geraniol. The overall radiochemical yield from acetone-2-^{14}C was 46 %.

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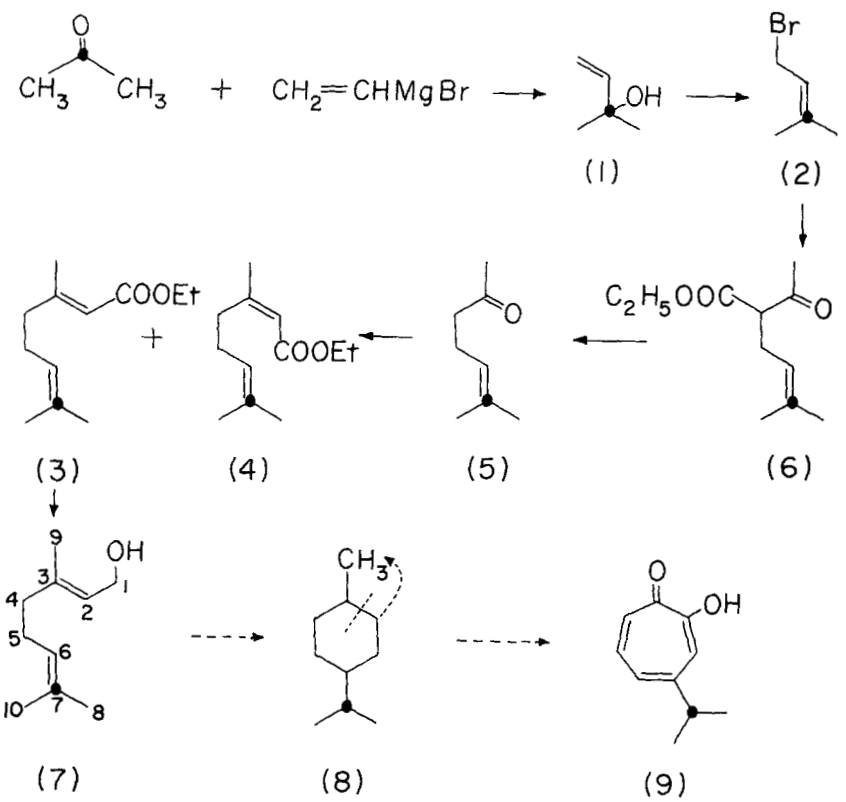
In preliminary experiments this geraniol-7-^{14}C was emulsified in water with the aid of a little Tween 80 and placed in a hole which had been drilled into the trunk of a 2 meter high *Thuja plicata* tree. The β-thujaplicin isolated 4 weeks later from the heartwood of the tree was not radioactive, although activity was detected in the terpene fraction from the plant. Experiments involving longer feeding times are being carried out.

Experimental.

2-Methyl-3-buten-2-ol-2-^{14}C (1).

Acetone-2-^{14}C (purchased from International Chemical and Nuclear Corporation, Calif.) (44 mg, 1.0 mCi) was diluted with non-radioactive acetone (0.2 g) and dissolved in dry tetrahydrofuran (5 ml). This solution was added slowly to a stirred solution of vinyl magnesium bromide in tetrahydrofuran (6 ml of a 1.88 M solution) [8], cooled to 0°. After stirring the mixture for 6 hours at room temperature, it was treated with a saturated aqueous



solution of ammonium chloride (7 ml). The aqueous layer was separated, diluted with a saturated sodium chloride solution (10 ml) and extracted with ether (3 × 10 ml). The organic layers were combined and washed with saturated salt solution (3 × 5 ml), and then dried over magnesium sulfate. The filtered extract was distilled through a short Vigreux column to remove most of the diethyl ether. The residual 2-methyl-3-buten-2-ol-2-^{14}C, dissolved in tetrahydrofuran (about 10 ml) was used in the next step without further purification.

3,3-Dimethylallyl bromide-3-^{14}C (2).

Pyridine (0.15 g) was added to the tetrahydrofuran solution of 2-methyl-3-buten-2-ol which was added slowly to a well stirred solution of phosphorus tribromide (0.4 g) in pentane (3 ml) cooled to −10°. After stirring for 2 hours at −10° a voluminous white precipitate had formed in the reaction mixture which was then added to water (30 ml) and extracted with pentane (3 × 30 ml). The combined pentane extract was washed with 5 % sodium carbonate, 5 % hydrochloric acid, and finally with saturated salt solution. The dried (magnesium sulfate) pentane solution was distilled yielding 3,3-dimethylallyl bromide as a pale yellow oil.

6-Methyl-5-hepten-2-one-6-^{14}C (5).

Ethyl acetoacetate (1.6 g) was added to a solution of sodium (0.23 g) in absolute ethanol (20 ml). The 3,3-dimethylallyl bromide, obtained in the previous step, was added dropwise to this solution stirred at room temperature. The mixture was refluxed for 12 hours and then 50 % aqueous potassium hydroxide (1 ml) was added and the refluxing continued for a further 2.5 hours. The cooled reaction mixture was acidified with 25 % sulfuric acid and diluted with water (30 ml) and extracted with ether (5 × 20 ml). The ether extract was washed with saturated salt solution (3 × 30 ml) and dried over magnesium sulfate. Evaporation yielded a colorless oil, gas chromatography indicating the presence of three compounds, one of which corresponded to the desired ketone. The crude reaction product was dissolved in petroleum ether (bp 60-70°) and chromatographed on a column of Woelm alumina (Activity I) (60 g). Elution of the column with 5 % chloroform in petroleum ether afforded 6-methyl-5-hepten-2-one-6-^{14}C chromatographically pure.

cis and *trans- Ethyl 3,7-dimethyl-2,6-octadienoates-7-^{14}C* (4) and (3).

The previously described ketone was dissolved in dimethoxyethane (3 ml) and added to a solution of triethylphosphonacetate (2.24 g) in dimethoxyethane (15 ml) which had previously been cooled and allowed to react with sodium hydride (0.415 g of a 58 % dispersion in mineral oil). The mixture was stirred at 55-60° for 24 hours in a nitrogen atmosphere. Water (10 ml) was then added to the cooled reaction mixture and extracted with ether

(5 × 15 ml). The ether extract was washed with 10 % sodium hydroxide, water, and salt solution. Evaporation of the dried (magnesium sulfate) ether extract yielded an oil which was subjected to thin layer chromatography on a preparative plate of Silica Gel-PF_{254} (Merck). The plate was developed five times in a 1 : 1 mixture of benzene and petroleum ether. The faster moving zone was the *cis*-isomer. The zones were extracted with 50 ml of a 5 % solution of methanol in methylene chloride. The ratio of *cis* to *trans* isomers obtained was 1 : 4.

Geraniol-7-^{14}C (7).

The previously obtained *trans*- ester was dissolved in ether (5 ml) and added slowly to a 4 % solution of lithium aluminum hydride in ether (3 ml) cooled to −78°. After stirring for one hour at −78° the mixture was allowed to warm to room temperature and stirred for 2 hours. Saturated ammonium chloride solution (10 ml) was added and the ether layer separated, washed with salt solution and dried over magnesium sulfate. Evaporation of the ether afforded geraniol-7-^{14}C as an almost colorless oil (271 mg, 46 % yield). Gas chromatography indicated that it was > 99 % pure and free of any nerol. It had a specific activity of 0.26 mCi/mM. It was stored as a solution in pentane (10 ml) at −20°.

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