A SYNTHESIS OF CAMPHENE-8-^{14}C AND TOXAPHENE-^{14}C

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SUMMARY

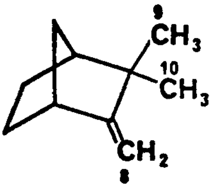
An efficient, one-vessel synthesis of camphene-8-^{14}C was developed. Methyl-^{14}C iodide was reacted with triphenylphosphine; treatment of the resulting phosphonium salt with methyllithium produced methylene[-^{14}C]-triphenylphosphorane, which was condensed with camphenilone to provide camphene-8-^{14}C. Chlorination of the latter compound produced toxaphene-^{14}C, an important polychlorinated insecticide.

Key Words: Toxaphene-^{14}C, Camphene-8-^{14}C, Insecticide, Wittig Reagent

INTRODUCTION

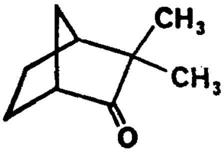
Toxaphene, a widely used insecticide [about 58 million lb/yr. in the United States (1)], is a complex mixture of at least 177 polychlorinated hydrocarbons (2) that is prepared by chlorinating camphene (I, 2,2-dimethyl-3-methylenebicyclo-[2.2.1]heptane) in the presence of ultraviolet irradiation until the chlorine content reaches 67-69% (average composition $C_{10}H_{10}Cl_8$). Our studies of toxaphene required a small amount of ^{14}C-labelled material of high specific activity.

Syntheses of both camphene-10-^{14}C (3) and camphene-8-^{14}C (II)(4) have been described. The former was a multi-step synthesis beginning with the incorporation of 0.226 mCi of sodium cyanide-^{14}C into 2 moles of ethyl acetoacetate cyanohydrin. The latter was a much simpler process. Methyl-^{14}C iodide was converted to the Grignard reagent which was in turn added to camphenilone (III, 3,3-dimethylbicyclo[2.2.1]heptan-2-one). The resulting tertiary alcohol was converted, via pyrolysis of its benzoate, to II. The overall yield from 30.8 g (0.5 mCi) of methyl iodide was ca. 60%, but the two distillations involved rendered this procedure of little value for the small scale (2 mmol) synthesis we wished to achieve.



I

II 8-^{14}C



III

$$^{14}CH_3I + Ph_3P \longrightarrow \underset{IV}{Ph_3\overset{\oplus}{P}\text{-}^{14}CH_3\overset{\ominus}{I}} \xrightarrow{BuLi} \underset{V}{Ph_3P{=}^{14}CH_2} \xrightarrow{III} II$$

$$II + Cl_2 \xrightarrow{h\nu} {}^{14}C\text{-toxaphene}$$

We therefore developed an alternate synthesis wherein the entire conversion of III to II was achieved in a single vessel. Methyl-^{14}C iodide (5 mCi, 0.5 mmol) was reacted with a slight excess of triphenylphosphine in tetrahydrofuran. The resulting methyltriphenylphosphonium iodide IV was converted to the Wittig reagent V with methyllithium. Treatment of V with III gave, after column chromatography, a solution (CCl_4) of essentially pure (by gas chromatography) II that was then irradiated and treated with chlorine; the reaction was followed by gas chromatographic analysis of aliquots, and was terminated (after ca. 7 hr.) when the gas chromatogram of the product approximated that of commercial toxaphene. Toxaphene-^{14}C (554 mg, 3.4 mCi, 68% overall) was isolated as a colorless wax.

EXPERIMENTAL

Methyl-^{14}C iodide was purchased from New England Nuclear Co. Radioactivity was measured with a Searle Mark II Scintillation Counter using a PPO/POPOP/toluene cocktail. Camphene samples were analyzed on a Varian aerograph Series 2700 gas chromatograph with a flame ionization detector and a 1.8 m x 2 mm stainless steel column packed with 3% OV-17 on Gas-Chrom Q, temperature programed from 95 to 140°. Toxaphene samples were analyzed on a Hewlett Packard 5709A gas chromatograph equipped with a ^{63}Ni-electron capture detector and a 1.8 m x 4 mm column packed with 1:1 15% QF-1 and 10% DC-200 on Chromasorb W at 215°. Triphenylphosphine and camphenilone were purified by sublimation in vacuo. Tetrahydrofuran was distilled from lithium aluminum hydride (under N_2) just prior to use, and was subsequently transferred by syringe through serum stoppers. Reaction vessels were oven-dried at 120°, then were assembled and purged with N_2 while hot. Syringes, needles, etc. were similarly dried at 120° then cooled to room temperature in a desiccator.

Camphene-8-^{14}C. Triphenylphosphine (600 mg, 2.3 mmol) was added to a 25 ml flask with a side arm and containing a micro stir bar. An overpressure of dry nitrogen was applied to the side arm, and the top of the vessel was fitted with a serum stopper. Methyl-^{14}C iodide (5 mCi, 50.7 mg, 0.36 mmol) was dissolved in tetrahydrofuran (8.0 ml), and the solution was injected into the reaction vessel. Then unlabelled methyl iodide (232 mg, 1.64 mmol) was added, and the resulting solution was stirred at room temperature for 5 hours. Methyltriphenylphosphonium iodide gradually separated as a white solid. The mixture was then cooled to ca. 5°, and a solution of methyllithium in ether (2.1 M, Aldrich Chemical Co.) was added dropwise by syringe (1.2 ml past the development of a permanent orange color). The resulting orange solution was stirred without cooling for 15 min., then was again cooled and treated with a solution of camphenilone (400 mg, 2.9 mmol), in tetrahydrofuran (5 ml). The resulting solution was stirred at room temperature overnight during which time solid triphenylphosphine oxide separated. The reaction mixture was poured into water (50 ml) and the resulting mixture was extracted with CCl_4 (3 x 6 ml). The combined organic extracts were washed with water and with 10% sodium thiosulfate, then were dried ($MgSO_4$), filtered, and concentrated by careful distillation through a 10 cm column to a final volume of ca. 5 ml. An additional 5 ml of CCl_4 was added, and distillation was resumed until the final volume was 3-4 ml (the distillation is fairly critical; tetrahydrofuran must be removed because it would provide unwanted chlorination products in the next step, but at the same time one has to be careful not to lose the relatively volatile camphene). The final residue was transferred onto a column of silica gel (16 g) prepared with CCl_4, and the column was eluted with CCl_4. The first 10 ml was discarded, and camphene-^{14}C was collected in the next 40 ml (> 98% free of camphenilone and other impurities by gas chromatography).

Toxaphene-^{14}C. The CCl_4 solution of camphene-^{14}C was stirred with a little activated charcoal then was filtered through Celite (previous experience showed that this treatment removed an unidentified substance which inhibited the chlorination reaction). Chlorine was slowly bubbled through the resulting solution in a Pyrex flask equipped with a condenser and a $CaSO_4$ drying tube; meanwhile the solution was irradiated with a dual-tube Westinghouse fluorescent sunlamp positioned 6 cm from the flask. The reaction was followed by periodically removing aliquots and comparing their gas chromotograms to one of a commercial toxaphene sample. After about six hr. the rate of chlorination had slowed to such an extent that the solution was again treated with charcoal and filtered through Celite. Chlorination now proceeded rapidly; after 45 min. the gas chromatogram was very similar to that of the standard, and the reaction was terminated. The solution was poured into a mixture of ice and aq. $NaHCO_3$; the layers were separated and the organic phase was washed again with $NaHCO_3$, then with 10% $Na_2S_2O_3$, and finally with H_2O. The solution was dried ($MgSO_4$) and filtered; removal of the solvent provided 0.554 g of toxaphene-^{14}C as a colorless wax (3.4 mCi).

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