SYNTHESIS OF ^{14}C-LABELED 2,4,2',5'-TETRACHLOROBIPHENYL

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SUMMARY

A synthetic procedure for 2,4,2',5'-tetrachlorobiphenyl-1,2,3,4,5,6-$^{14}C_6$ is presented. 2,4-Dichloroaniline-$^{14}C_6$ was prepared in 46.7% yield from benzene-$^{14}C_6$ via m-dinitrobenzene-$^{14}C_6$, m-dichlorobenzene-$^{14}C_6$ and 2,4-dichloronitrobenzene-$^{14}C_6$. 2,4-Dichloroaniline-$^{14}C_6$ was coupled with p-dichlorobenzene to produce ^{14}C-labeled tetrachlorobiphenyl. The yield was 21% based on 2,4-dichloroaniline-$^{14}C_6$.

Key Words: 2,4-Dichloroaniline, 2,4,2',5'-Tetrachlorobiphenyl, Carbon-14.

INTRODUCTION

Since polychlorinated biphenyls (PCBs) were recognized as one of the most important pollutants in the environment, they have received wide attention on their various effects on living things. In order to facilitate biological studies of PCBs, their radioactive forms had been much required. The author and his coworker had prepared several kinds of ^{14}C-labeled PCB mixtures and put them to practical use[1]. Using these labeled PCBs, Shimada studied metabolism of PCBs to elucidate mechanism by which PCBs induce liver injury[2]. For further detailed study, ^{14}C-labeled individual constituents of PCBs including 2,4,2',5'-tetrachlorobiphenyl have come to be required. Up to date, however, only a limited number of the radioactive syntheses have been published in the literature[3-6]. This may be due partly to limitation of availability of the starting materials.

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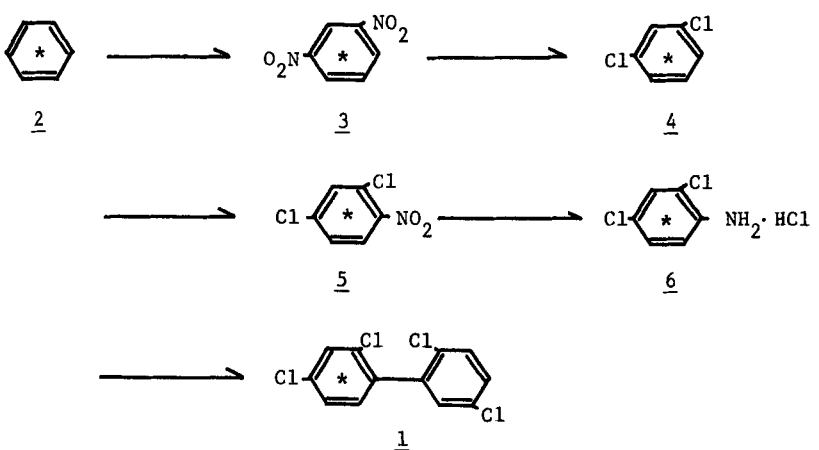
The author has started a program for the synthesis of ^{14}C-labeled individual chlorinated biphenyls. First of all, the present work was undertaken to meet the need for 2,4,2',5'-tetrachlorobiphenyl-^{14}C. As unsymmetrical biphenyls are generally prepared from corresponding chloroanilines and excess of chlorobenzenes[7-10] and no attractive alternative method can be found, 2,4-dichloroaniline-^{14}C was necessary for the present purpose. This labeled compound had previously been prepared in 35% yield by chlorination of commercial aniline-^{14}C with potassium chlorate[3].

The author sought a practical synthetic route for this compound starting from less expensive benzene-$^{14}C_6$. The following scheme was devised by modifying the known methods for non-labeled compounds. 2,4-Dichloroaniline-$^{14}C_6$ (6) was then coupled with p-dichlorobenzene to produce 2,4,2',5'-tetrachlorobiphenyl-1,2,3,4,5,6-$^{14}C_6$ (1) according to the published procedure[10].



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EXPERIMENTAL

Benzene-$^{14}C_6$ used as a starting material was previously prepared from barium carbonate-^{14}C according to the published method[12]. The yield and the purity of the products at each stage were determined by radio-gaschromatography (YANAKO G-1800 GLC equipped with a combustion train, a drying tube and a GM counting cell). Radioactivity was measured by liquid scintillation counting (Beckman LS-100). The final product was identified by UV spectrometry (Hitachi EPU-2), mass spectrometry (Hitachi RMU-6MG GLC-MS) and measurement

of melting point (Micro hot stage, uncorrected). Retention time relative to 1,1'-dichloro-2,2'-bis(p-chlorophenyl) ethylene (p,p'-DDE) was also compared with that of the authentic 2,4,2',5'-tetrachlorobiphenyl.

m-Dinitrobenzene-$^{14}C_6$ (3)--- Benzene-$^{14}C_6$ (2) (2 mmol, 22.5 mCi) was transferred under vacuum to a Pyrex glass tube containing KNO_3 (0.7 g) and conc H_2SO_4 (1.6 ml) chilled with liquid nitrogen and sealed. After being allowed to warm to the room temperature, the contents were mixed well and the tube was heated at 80° for 1 hr with occasional shaking. Then, the tube was opened in a vacuum line to remove the volatile contents. The residual liquid was poured into ice water and the precipitate formed was collected by filtration, followed by washing with water and dried in a vacuum desiccator. The radiochemical yield was 82% (278 mg, 18.5 mCi).

m-Dichlorobenzene-$^{14}C_6$ (4)--- m-Dinitrobenzene-$^{14}C_6$ (3) (278 mg, 18.5 mCi) was placed in a Pyrex glass tube and dried CCl_4 (1.5 ml) was added to it. After the contents had been cooled with Dry Ice, the tube was sealed, placed in an electrical furnace kept at 280° and heated for 1 hr. The tube was then chilled with liquid nitrogen and opened. The gaseous contents and the excess CCl_4 were removed by evaporation. To the residual liquid, a small amount of pentane was added and the solution was poured onto a column of silica gel (Merck, 70-230 mesh, 12 x 150 mm). m-Dichlorobenzene-$^{14}C_6$ (4) was eluted with 50 ml of pentane. Evaporation of the solvent gave a colorless 4 with a radiochemical purity of 97%. The radiochemical yield was 86% (210 mg, 15.9 mCi, Specific activity 11.1 mCi/mmol).

2,4-Dichloronitrobenzene-$^{14}C_6$ (5)--- m-Dichlorobenzene-$^{14}C_6$ (4) (210 mg, 15.9 mCi) was transferred with a small amount of ether to a Pyrex glass tube, the solvent was removed by evaporation, conc H_2SO_4 (0.3 ml) was added and mixed well. Then, 0.3 ml of 1:1 mixture of HNO_3 (sp. gr. 1.40) and 96% H_2SO_4 was added dropwise. The tube was then cooled with Dry Ice, sealed and warmed

at 40° for 1hr with shaking. After cooling with Dry Ice, the tube was opened and the reaction mixture was neutralized with conc NaOH solution. The solution was extracted several times with ether. The combined extracts were washed with water and dried over $CaCl_2$. Evaporation of the solvent gave a crude 5 with a radiochemical purity of 90%. The only impurity detected was unreacted 4 . The crude 5 was dissolved in a small amount of pentane/ether (95:5) and the solution was poured onto a column of silica gel (Merck, 70-230 mesh, 12 x 150 mm). After m-dichlorobenzene-$^{14}C_6$ (4) had been eluted with pentane in the way as described above, the product 5 was eluted in small fractions with pentane/ether (95:5). The desired fractions were collected and evaporation of the solvent gave a radiochemically pure 5 . The radiochemical yield was 81% (225 mg, 12.8 mCi, Specific activity 10.9 mCi/mmol).

2,4-Dichloroaniline-$^{14}C_6$ hydrochloride (6)--- 2,4-Dichloronitrobenzene-$^{14}C_6$ (5) (225 mg, 12.8 mCi) was dissolved in 5 ml of warm ethanol/water (60:40) in a 50 ml flask equipped with a reflux condenser. Granulated tin (2.5 g) was added to the solution and the mixture was warmed at 50° for 10 minutes. Concentrated HCl (2.5 ml) was added portionwise and the reaction mixture was refluxed for 30 min. Then conc NaOH solution was added to make the solution alkaline. After cooling, the solution was extracted several times with ether and the combined extracts were dried over $CaCl_2$. Hydrogen chloride gas dried through conc H_2SO_4 was then introduced into the ethereal solution and the precipitate of 6 formed was collected by filtration and dried in a desiccator (242 mg, 9.5 mCi). Pure 2,4-dichloroaniline (60 mg) was added as a carrier to the filtrate and the precipitate was obtained again in the same way (72 mg, 1.0 mCi). The total radiochemical yield was 82%. Both products, presumably contaminated with excess of hydrogen chloride, were combined and a portion of them was converted to 2,4-dichloroaniline-$^{14}C_6$ by treatment with NH_4OH, followed by extraction with ether. The specific activity of 2,4-dichloroaniline-$^{14}C_6$, determined by gaschromatography and radioactivity measurement of an aliquot of the ethereal solution, was 8.75 mCi/mmol. Radio-gaschromatographic

analysis showed to be radiochemically pure.

2,4,2',5'-Tetrachlorobiphenyl-1,2,3,4,5,6-$^{14}C_6$ (1)--- 2,4-Dichloroaniline-$^{14}C_6$ hydrochloride (6) (300 mg, 10.0 mCi) was mixed with non-radioactive 2,4-dichloroaniline (180 mg) and p-dichlorobenzene (10 g) in a 50 ml flask equipped with a reflux condenser. The mixture was heated at 70° in an oil bath until p-dichlorobenzene melted. To the resulting suspension, isoamyl nitrite (1.0 ml) was added with vigorous stirring. The temperature was slowly raised to 130° and kept there for 1 hr. Excess p-dichlorobenzene was then removed by distillation under a pressure of about 700 Torr at 200°. The residue was dissolved in a small amount of hexane and the solution was poured onto a column of silica gel (Merck, 70-230 mesh, 12 x 250 mm). On the elution with hexane, the product 1 was eluted over 10 ml fractions from fourth to eighth, among which the fifth and sixth fractions containing pure 1 (checked by GLC) were collected. Other impure fractions were combined, concentrated and the same chromatographic separation was performed again. Next, pure 2,4,2',5'-tetrachlorobiphenyl (50 mg) was added as a carrier to the combined impure fractions and the same separation procedure was repeated. The latter procedure using 50 mg of the carrier at a time was repeated two more times. The fractions containing pure 1 from each run were combined and the solvent was evaporated to leave an almost colorless oil which crystallized on standing. This was recrystallized from methanol/water (95:5). The radiochemical yield was 21% (204 mg, 2.1 mCi, Specific activity 3.0 mCi/mmol).

M.p. and mixed m.p.: 64.0-64.5°; UV (EtOH): λ_{max}275nm (logε 3.12), 282nm (logε 3.09); GLC-MS: M^+ 290($C_{12}H_6{}^{35}Cl_4$), 292($C_{12}H_6{}^{35}Cl_3{}^{37}Cl$), 294($C_{12}H_6{}^{35}Cl_2{}^{37}Cl_2$) 296($C_{12}H_6{}^{35}Cl^{37}Cl_3$), 298($C_{12}H_6{}^{37}Cl_4$); Relative retention time (p,p'-DDE = 1.00): 0.446.

DISCUSSION

In the route presented here, the reaction steps 1, 3 and 4 were readily accomplished by the conventional methods with minor modifications.

For the substitution of the nitro groups by chlorine (Step 2), an initial attempt was made with thionyl chloride[5]. But the yields varied widely (55-83%) probably because this reaction is very sensitive to the presence of moisture. Instead, carbon tetrachloride was used in this work[11]. This was found to be preferable from both viewpoints of yield and handling procedure. The reaction was achieved simply by heating the reaction mixture in a sealed tube. An important factor of this reaction was the temperature; excellent yields were obtained at 280°. On the other hand, when it exceeded 290°, yields decreased by the formation of considerable amounts of trichlorobenzenes as by-products which were impossible to remove by the simple procedure as described in the experimental section. The reaction time was also varied from 30 to 90 minutes. The yields reached nearly 90% in 60 minutes and did not alter during additional 30 minutes.

In the trial experiments for the synthesis of 2,4,2',5'-tetrachlorobiphenyl, the reaction yields were always about 30%, but only about 60% of the product could be obtained in pure state even by repeating column chromatography. Therefore, in the hot run, addition of carrier 2,4,2',5'-tetrachlorobiphenyl was required to aid separation procedure. To avoid uncontrolled isotopic dilution with a carrier, the quantity and radioactivity of the labeled products both in the pure and in the impure fractions were checked each time when the carrier was to be added.

The radiochemical purity of the purified product, determined by radiogaschromatography, was greater than 98%. UV spectrum, mass spectrum and other data were all identical to those of the authentic 2,4,2',5'-tetrachlorobiphenyl.

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