

Metabolism of Insecticides

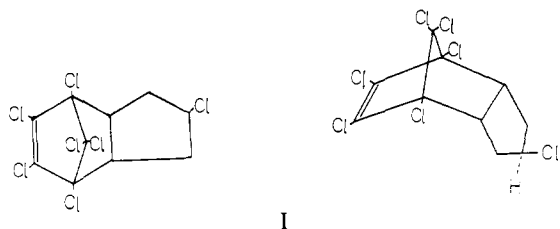
Microsynthesis of ^{14}C - β -Dihydroheptachlor

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Synthesis of ^{14}C - β -dihydroheptachlor was achieved on a microscale to investigate its metabolism. The procedure for hydrochlorination of chlordene

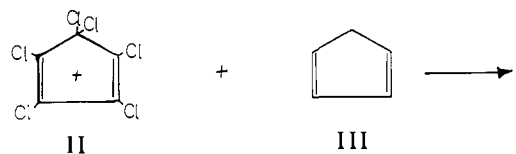
was modified to suit the microscale. Over-all chemical yield was 84%.

To study the metabolism of chlorinated insecticides, ^{14}C - and ^{36}Cl -labeled insecticides have been prepared (Brooks, 1958; Burton and Potter, 1959; Korte and Rechmeier, 1962; McKinney and Pearce, 1960; Perry, 1960; Rechmeier, 1962). Recently, Büchel *et al.* (1964) reported that a compound with a structure similar to that of heptachlor possesses low mammalian toxicity but an insecticidal value similar to that of DDT and chlordan.



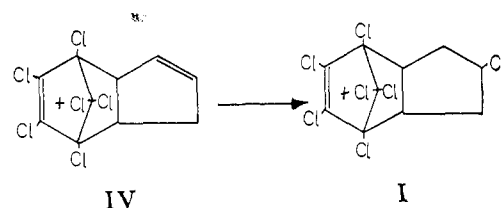
This compound, 2-*exo*-4,5,6,7,8-heptachloro-4,7-methano-3 α ,4,7,7 α -tetrahydroindan commonly known as β -dihydroheptachlor (I) was prepared with a ^{14}C label. Synthesis of β -dihydroheptachlor has been worked out in detail (Büchel *et al.*, 1966a), but unfortunately some of the conditions employed on a macroscale were impractical on a 200-mg. scale or under.

^{14}C -Hexachlorocyclopentadiene (II) in benzene solution (Radio Chemical Centre, Amersham, England, specific activity, 70.7 mc. per mmole) was diluted with freshly distilled hexachlorocyclopentadiene. Nearly 75% excess of freshly distilled cyclopentadiene (III) was added to get higher yields of ^{14}C -chlordene (IV). Reaction between hexachlorocyclopentadiene and cyclopentadiene occurred without the use of any solvent. Addition of 1 to 2 mg. of hydroquinone reduced the reaction time and facilitated crystallization. Generally, hydrochlorination of chlordene is carried out under pressure. This yields α , β , and γ isomers of dihydroheptachlor. The α and γ forms were shown to isomerize to the more potent β form (Büchel *et al.*, 1966b). However, an 88% yield of β -dihydro-



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+ Position of ^{14}C label in the compound

heptachlor was obtained in one step by gently bubbling dry hydrogen chloride through a solution of chlordene in 1,2-dichloroethane which had been stored over potassium hydroxide. Sublimed ferric chloride (10%, w./w. of chlordene) was used as the catalyst. Generally, much lower concentrations of ferric chloride (4%, w./w. of chlordene) were used and the hydrochlorination was carried out under high pressure. For the microscale synthesis at atmospheric pressure, this quantity was inadequate. During this step, all chemicals used must be absolutely free from water, as traces of water affect the yield of the end product and often there is no hydrochlorination at all.

EXPERIMENTAL

Synthesis of ^{14}C -Chlordene. A vial containing 2.0 mc. of ^{14}C -hexachlorocyclopentadiene in benzene solution was opened, and its contents were transferred into a 10-ml. tube with a ground glass stopper. Benzene was evaporated by blowing a gentle stream of nitrogen over the surface. The residue was then diluted to 123 mg. (0.45 mole) with freshly distilled hexachlorocyclopentadiene. Hydroquinone (1 to 2 mg.) was added as catalyst. To this, 53 mg. of freshly distilled cyclopentadiene (0.8 mole) was added. The tube was then closed. Only the lower portion of the tube containing the reacting compounds was immersed in an oil bath. The crystallization of ^{14}C -chlordene began after about 90 minutes, but the heating was continued for 6 hours. The tube was then opened and heated for another 30 minutes to eliminate excess cyclopentadiene. ^{14}C -Chlordene was then purified by sublimation in vacuum at 90° C. Theoretical yield 152 mg., practical yield 144 mg. (95% of theoretical yield).

Synthesis of ^{14}C - β -Dihydroheptachlor. ^{14}C -Chlordan (144 mg.) was dissolved in 2 ml. of water-free 1,2-dichloroethane in a small tube. Sublimed ferric chloride (14 mg.) was added, and dry hydrogen chloride was slowly bubbled through the solution. The tube was immersed in a metal bath at 160° C. for 4 hours. Excess hydrochloride was absorbed in a solution of sodium hydroxide.

The ^{14}C - β -dihydroheptachlor was purified by thin-layer chromatography. The over-all chemical yield was

84% (141 mg.; specific activity, 4.4 mc. per mmole; m.p. 133° C., m.p. of authentic nonradioactive sample, 135° C.)

Thin-Layer Chromatography. Fifty grams of silica gel (Merck) was shaken with 100 ml. of distilled water for about 1 minute, and the suspension was spread evenly (0.3 mm. thick) on smooth glass plates. The plates were then allowed to dry in air for about 15 minutes and were subsequently activated by heating at 100° C. for 30 minutes. The plates were allowed to cool to room temperature in a desiccator, and the entire quantity was chromatographed. The position of ^{14}C - β -dihydroheptachlor was detected by cochromatography of an authentic sample on blancophore plates and the corresponding zones were scraped from normal plates after autoradiography.

Unreacted ^{14}C -chlordane and ^{14}C - β -dihydroheptachlor were present as impurities. These were removed and the silica gel containing pure ^{14}C - β -dihydroheptachlor was extracted with ether in a Soxhlet extractor. Purity of the compound was again checked by radiochromatography and cochromatography with authentic samples on blancophore plates.

For cochromatography, blancophore solution was used instead of distilled water. On freshly prepared plates

with blancophore solution, the spots were clearly visible in ultraviolet light. As mobile phase, *n*-hexane was generally used.

Blancophore Solution. Blancophore solution was prepared by dissolving 10 mg. of Blancophore (Tschesche *et al.*, 1963) in 100 ml. of distilled water.

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