SYNTHESIS OF ^{14}C-ENDOSULFAN FROM 2,3 ^{14}C-MALEIC ANHYDRIDE

K. L. Huhtanen and H. W. Dorough*
Department of Entomology, University of Kentucky
Lexington, Kentucky 40506, U.S.A.
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SUMMARY

The insecticide endosulfan (5a,9a-^{14}C 6,7,8,9, 10,10-hexachloro-1,5,5a,6,9,9a hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide) was prepared from 2,3 ^{14}C-maleic anhydride. The Diels-Alder reaction of maleic anhydride with hexachlorocyclopentadiene yielded 1,4,5,6,7,7-hexachlorobicyclo [2.2.1] hept-5-ene-2,3-dicarboxylic acid anhydride. This anhydride was reduced to the corresponding carboxylic acid γ lactone with sodium borohydride which was further reduced to the diol (1,4, 5,6,7,7-hexachloro-2,3-bis-(hydroxymethyl) bicyclo [2.2.1] hept-5-ene) with lithium aluminum hydride. The later compound was reacted with thionyl chloride in carbon tetrachloride to give endosulfan.

Key Words: Endosulfan, Diels-Alder, Maleic Anhydride, Hydride Reduction, Carbon-14

INTRODUCTION

The synthesis of ^{14}C-endosulfan by Forman (1) employed the Diels-Alder reaction between hexachlorocyclopentadiene (HCCP) and 2,3 $^{14}C_2$ cis-2-butene-1, 4-diol diacetate. This synthesis involved a lengthy preparation of the 2,3 ^{14}C cis-2-butene-1,4-diol. A more convenient route to ^{14}C-labeled diol (1,4,5,6,7,3-hexachloro-2,3-bis-(hydroxymethyl)-bicyclo-[2.2.1]-hept-5-ene), the precursor of endosulfan, was described by Korte and Stiasni (2) in their radiosynthesis of the insecticide Telodrin. In that preparation, ^{14}C-maleic anhydride was the dienophile in the Diels-Alder reaction with HCCP yielding anhydride (1,4,5,6,7,7-hexachlorobicyclo [2.2.1] hept-5-ene-2,3-dicarboxylic acid anhydride). The anhydride was then hydrolyzed to the dicarboxylic acid, methylated with diazomethane, and reduced with lithium aluminum hydride to the diol.

* To whom correspondence should be addressed.
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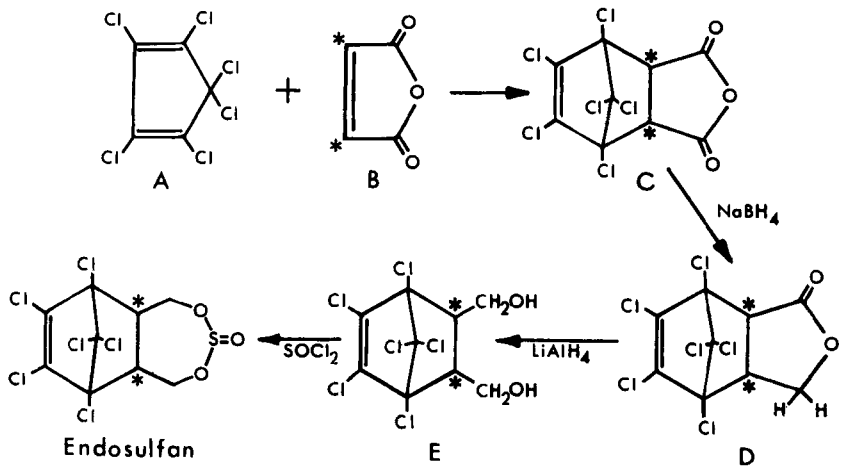

Figure 1. Synthesis of ^{14}C-endosulfan. Asterisk indicates position of radiocarbon.

In our laboratory, the preparation of the dimethyl ester from the diacid using diazomethane gave very low yields. Therefore, the lithium aluminum hydride reduction of the diacid to diol as described by Riemschneider and Hilscher (3) was attempted. However, the small quantities of diacid used in the reaction prevented satisfactory yields of the diol. Despite these problems, the commercial availability of ^{14}C-labeled maleic anhydride as a convenient starting material prompted our continued investigation of its use in the synthesis of endosulfan.

EXPERIMENTAL

Reagents

2,3 ^{14}C-Maleic anhydride was purchased from the California Bionuclear Corporation. The sodium borohydride was obtained from Fisher Scientific Company and the thionyl chloride and lithium aluminum hydride from Matheson Coleman and Bell Company. The alpha and beta endosulfan standards were from Niagara Chemical Division of FMC Corporation. A standard of the lactone

(4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-4,7-methanisobenzofuran-1 (3H)-one) was prepared from the anhydride (18.4 g, 0.05 moles) by sodium borohydride reduction according to the method of Bailey and Johnson (4). The ether concentrate, a yellow oil, was recrystallized from 1:10 (v/v) water:methanol. A second recrystallization from ether:pentane gave 4.4 g (0.012 moles; 25% yield) of the lactone. The product's mp 261-263° (lit. (3) mp 263-4°); carbonyl infrared absorption at 1770 cm^{-1}.

An authentic sample of the diol (1,4,5,6,7,7-hexachloro-2,3-bis (hydroxymethyl)-bicyclo-[2.2.1] hept-5-ene) was prepared from the lactone. The lactone (200 mg, 0.56 mmoles) in 4 ml of THF (tetrahydrofuran) was added to 20 mg (0.53 mmoles) of lithium aluminum hydride contained in 2 ml of THF at 0°C. This solution was warmed to room temperature and shaken for 30 minutes. The solution was then poured over 4-6 g of ice and mixed with 8 ml of ethyl ether. The gelatinous material which formed was removed by vacuum filtration and the remaining water phase was washed with ether. After separating the water and ether layers, the water was saturated with sodium chloride and washed (2 x 25 ml) with ether. The combined ether fractions were dried over sodium sulfate, filtered and concentrated. The diol was recrystallized from ether:chloroform; mp 204° (lit. (3) mp 205-6°); its spectrum corresponded to Forman's (1); yield 180 mg (89%).

Preparation of ^{14}C-Endosulfan

One millicurie of 2,3 ^{14}C-maleic anhydride, specific activity 3.99 mCi/mM, was mixed with 76 mg of nonradioactive anhydride, giving a final specific activity of 0.98 mCi/mM. The maleic anhydride (Fig. 1, B) was dissolved in ether and transferred to a screw-top glass tube and the ether removed by evaporation with the aid of dry nitrogen. Hexachlorocyclopentadiene (Fig. 1, A; 279 mg, 1.02 mmoles) was added, followed by 100 µl of toluene, and the tube sealed with Teflon tape. After incubation at 100°C for 14 hrs, the mixture was cooled, and upon the addition of 2 ml of pentane, a white solid formed. The crude product containing the lactone (Fig. 1, C) was washed three times with pentane and the excess pentane removed from the solids under dry nitrogen. Dried tetrahydrofuran,

5 ml, was added and the resulting solution cooled to 0°C, and 40 mg of sodium borohydride (1.06 mmoles) added. After the initial reaction had subsided, the solution was shaken at room temperature for one hour. The solution was again cooled to 0°C before slow addition of 2 ml of 2 M HCl. Three 5-ml portions of ether were used to extract the lactone from the aqueous phase. The combined ether extracts were dried over sodium sulfate, concentrated under vacuum and the residue dissolved in 40 ml of dry benzene. Twenty five milliliters of benzene were distilled from the flask to remove any water as the azeotrope. The remaining benzene was removed under vacuum.

The solid residue was a mixture of reduction products and the lactone (Fig. 1, D) as determined by the infrared analysis. This crude product was dissolved in 5 ml of dry THF, cooled to 0°C, and added to 30 mg (0.79 mmoles) of lithium aluminum hydride in 2 ml of THF. The reaction mixture was held at 0°C for 15 min., after which it was shaken at 40°C for two hours. Following cooling to 0°C, the reaction mixture was poured over 4-6 g of ice, 8 ml of ether were added, with stirring and the mixture filtered. The ether layer was removed and the water again washed with ether. After separating the aqueous and ether layers, the water was saturated with sodium chloride and extracted twice with 25-ml portions of ether. The combined ether fractions were dried over sodium sulfate, filtered and concentrated to give approximately 230 mg of crude diol (Fig. 1, E). A sample of the product cochromatographed with a diol standard on silica gel plates (250 μ, F-254 Brinkmann) developed in 3:1 chloroform:ethyl-acetate; diol R_f = 0.55. The crude diol was partially dissolved in 8 ml of carbon tetrachloride to which was added 0.5 ml (0.82 g, 6.88 mmoles) of thionyl chloride. After heating at 55°C for 5 hours, the liquid phase was distilled from the final product, endosulfan.

The tlc of ^{14}C-endosulfan preparation along with standards showed that 86% of the radioactivity was associated with the two endosulfan isomers: the solvent system = 6:1 hexane:acetone; R_f beta = 0.32, alpha = 0.60. Autoradiography revealed four other products exhibiting R_f values of 0.45, 0.20, 0.11 and

0.06. The endosulfan isomers were extracted from the silica gel with ether and two-dimensional tlc used for verification of the purity of the isomers. The solvents used were 6:1 hexane:acetone and 1% ether in benzene. Radioassay of both isomers showed that 93% of the activity was coincident with the alpha and beta standards. The mass spectrum of the alpha isomer was identical to that of Hutzinger and Safe (5). The yield based on the radioassay of products was 60% of theoretical. The yield of individual isomers was 15% beta and 45% alpha endosulfan.

DISCUSSION

Although the isolation of nonradioactive lactone (Fig. 1, D) from the crude reaction mixture resulted in a rather unimpressive 25% yield, the crude product when further reduced with lithium aluminum hydride gave the diol (Fig. 1, E) in excellent yields. The preparation as described has given endosulfan yields of 50 to 60% from maleic anhydride on repeated preparations from nonradioactive materials. Obviously there was some loss of the lactone during attempts to isolate it from the crude reaction mixture.

The production of the diol is the most critical stage in the synthesis of milligram quantities of endosulfan. In our studies, complete reduction of the anhydride to the diol required two sequential reductive reactions. While Bloomfield and Lee (6) have successfully reduced methyl substituted homologues of cyclohex-4-ene-1,2 dicarboxylic acid anhydride to the diol using excess lithium aluminum hydride in refluxing THF, other products have been obtained from cyclic anhydride reductions. Marvel and Fuller (7) reported that succinic acid reduction with lithium aluminum hydride resulted in the formation of some γ lactone. Moreover, Granger and Techer (8) reported that cis-1-methylcyclohex-4-ene-1,2-dicarboxylic acid anhydride reduction with lithium aluminum hydride produced the lactone. Similar attempts to reduce the anhydride intermediate of endosulfan (Fig. 1, C) yielded only the lactone and, therefore, it was essential that different approaches be considered. It was subsequently found that

reduction of the anhydride with sodium borohydride, followed by lithium aluminum hydride reduction resulted in good yields of the diol intermediate. Once the diol was synthesized in sufficient quantities, the final step in the preparation of ^{14}C-endosulfan was easily accomplished by reacting the diol with thionyl chloride.

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