

A STUDY OF SUBSTITUTED DIPHENYLACETIC ACIDS

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A STUDY OF SUBSTITUTED DIPHENYLACETIC ACIDS

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CHAPTER I

INTRODUCTION

The high insecticidal activity of 2,2-bis-(4-chlorophenyl)-1,1,1-trichloroethane (DDT) and related products¹ has led to the synthesis of many types of compounds structurally related to DDT. Woodburn and Sroog² investigated the synthesis and insecticidal activity of a large group of chloroalkyl chlorobenzoates, including 2,2,2-trichloroethyl 4-chlorobenzoate. None of these compounds were active against the mexican bean beetle, greenhouse spider, the confused flour beetle, and German cockroach.

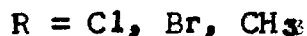
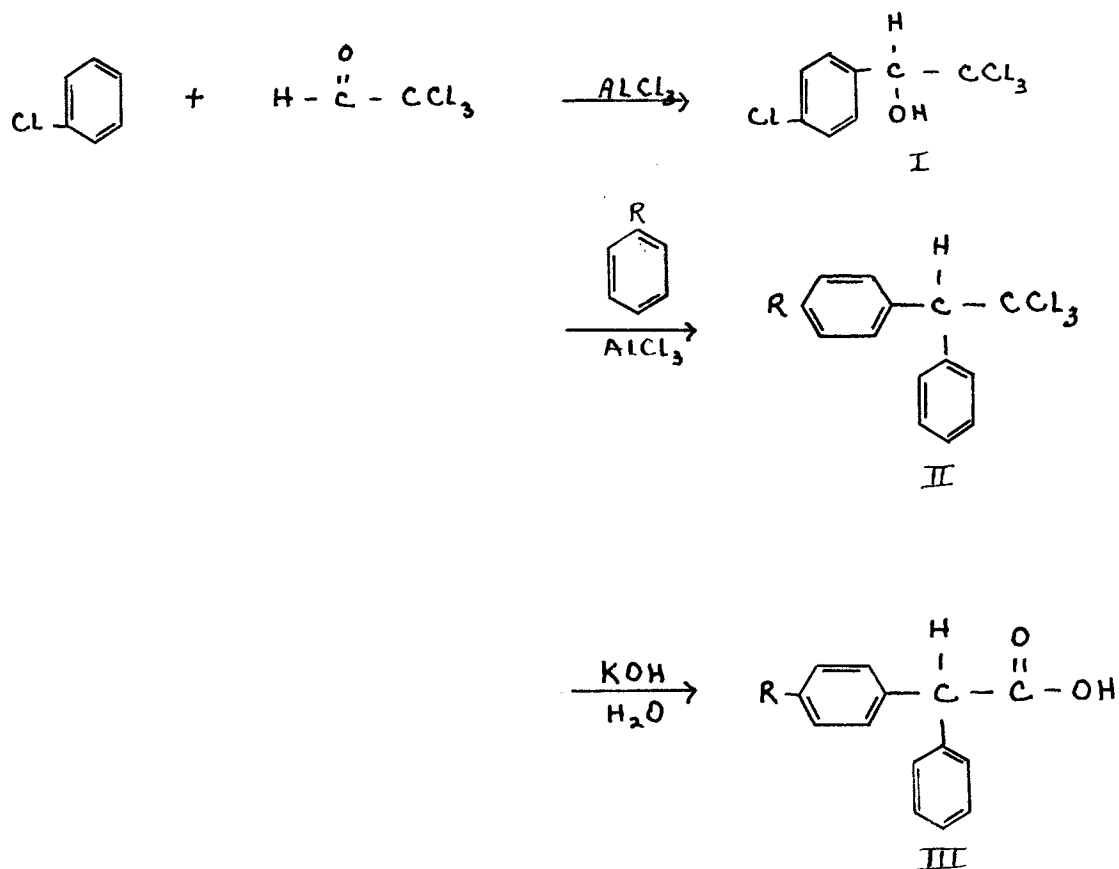
Despite the lack of activity of these compounds, it seemed worthwhile to synthesize various derivatives of the closely related 2,2-(4,4'-disubstituted) diphenylacetic acids (III). In order to find the effect of varying substituents in the phenyl rings, it was decided to make 2-(4-chlorophenyl)-2-(4-bromophenyl)acetic acid, 2-(4-chlorophenyl)-2-(4-tolyl)acetic acid, 2,2-bis-(4-chlorophenyl)acetic acid, and various derivatives.

(1) L. Lauger, H. Martin, and F. Muller, Helv. Chem. Acta., 27, 892 (1944).

(2) H. M. Woodburn and C. E. Sroog, J.A.C.S., 71, 1709 (1949).

The most direct route to these acids appeared to be to synthesize first the corresponding unsymmetrical analogs of DDT³ (II) and subsequently hydrolyze these compounds to the desired substituted diphenylacetic acids⁴ (III).

In addition to insecticidal action, the various derivatives of these acids might possess interesting physiological activity.



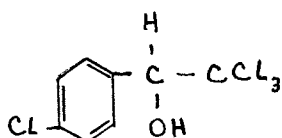
(3) G. H. Schneller and G. B. L. Smith, J. A. C. S., **70**, 4057 (1948).

(4) O. Grummitt, M. Buck, and C. Egan, Org. Syn., **26**, 21 (1946).

CHAPTER II

EXPERIMENTAL

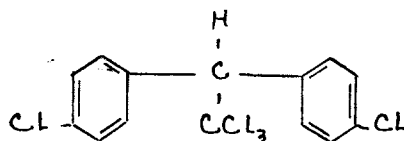
1-(4-Chlorophenyl)-1-hydroxy-2,2,2,-trichloroethane⁵



A mixture of 1000 g. of chlorobenzene and 200 g. of chloral was treated under vigorous stirring with 33 g. of freshly powdered anhydrous aluminum chloride, added in small amounts over a period of one hour. This mixture was allowed to stir for twelve hours. The reaction mixture was then allowed to stand for ten hours. The product mixture was poured into cold water and the oil washed with dilute hydrochloric acid and water. The chlorobenzene layer was separated and the excess chlorobenzene was distilled under vacuum. A good yield of thick, crude, black liquid was obtained. This compound was used in the crude form as the starting material for other reactions.

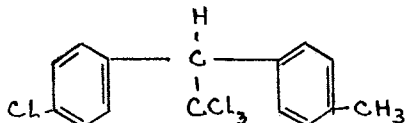
(5) von Leuthold, French Patent 791,172 (Dec. 5, 1935);
C. A., 30, 3157 (1936).

Preparation of DDT as Derivative to Check the
Structure of 1-(4-Chlorophenyl)-1-hydroxy-
2,2,2,-trichloroethane



A small, three-necked round-bottom flask was fitted with a mechanical stirrer, thermometer, and a dropping funnel. Twenty-six grams (0.1 mole) of 1-(4-chlorophenyl)-1-hydroxy-2,2,2,-trichloroethane were dissolved in 62 ml. of concentrated sulfuric acid and the solution was placed in the flask. With the temperature at 90°, 22.1 g. (0.2 mole) of chlorobenzene was added rapidly, followed by the dropwise addition of 50 ml. of concentrated sulfuric acid over a period of one and one-half hours. This mixture was then stirred for an additional six and one-half hours. The product mixture was poured over ice, and a light brown solid precipitated. The solid was filtered, washed until neutral to litmus paper, and dissolved in alcohol. The alcoholic solution was treated with Norite, filtered, and cooled. The crude product was recrystallized from alcohol, filtered, and dried. When pure it melted at 78°. DDT is reported to melt at 78°.

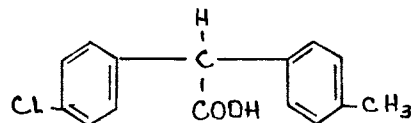
1,1,1-Trichloro-2-(4-chlorophenyl)-2-(4-tolyl)ethane



A small, three-necked, round-bottom flask was fitted with a mechanical stirrer, thermometer, and a dropping funnel. A solution of 26 g. (0.1 mole) of 1-(4-chlorophenyl)-1-hydroxy-2,2,2,-trichloroethane in 62 ml. of concentrated sulfuric acid was placed in the flask. With the temperature at 90°, 18.4 g. of toluene was added rapidly. This addition was followed by the addition of 50 ml. of concentrated sulfuric acid. This acid was added dropwise over a period of one and one-half hours. The product mixture was poured over ice, and a light brown solid precipitated. The solid was filtered, washed until neutral to litmus, and dissolved in alcohol. The alcoholic solution was treated with Norite, filtered, and cooled. The crude product was recrystallized from alcohol and dried. Long, clear, needle-like crystals were obtained, m. p. 84°. The yield was 82%.

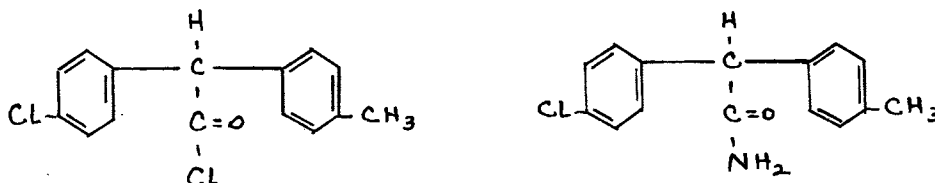
Anal. Calcd. for $C_{15}H_{12}Cl_4$: Cl, 42.5. Found: Cl, 42.2.

2-(4-Chlorophenyl)-2-(4-tolyl)acetic Acid



A mixture of 400 ml. of diethylene glycol and 46.8 g. (0.14 mole) of 1-(4-chlorophenyl)-1-tolyl-2,2,2,-trichloroethane was placed in a 1-l. flask fitted with a stirrer, reflux condenser and a thermometer. To this mixture was added a solution of 63 g. (1.12 moles) of potassium hydroxide in 35 ml. of water. The mixture was stirred and refluxed for six hours at a temperature of 134-137°. The mass was then allowed to cool and was poured into 1000 ml. of cold water, filtered, and the precipitate washed twice with warm water. The filtrate was boiled gently with 2 grams of Norite for five minutes. The solution was filtered and acidified to litmus paper with 20% sulfuric acid (approximately 120 ml.) and an additional 30 ml. of the acid was added. The mixture was then cooled to 0-5°, the precipitate filtered, washed free of the sulfate ions with water, and dried at 100-110°. A yield of 99.2% of pure product was obtained, m. p. 155°.

2-(4-Chlorophenyl)-2-(4-tolyl)acetyl Chloride and
2-(4-Chlorophenyl)-2-(4-tolyl)acetamide

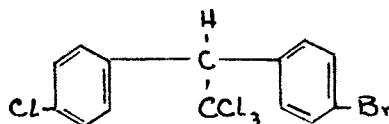


A mixture of 50.5 g. (0.2 mole) of 2-(4-chlorophenyl)-2-(4-tolyl)acetic acid and 20 ml. (32 g., 0.27 mole) of thionyl chloride was heated on a steam bath until the acid had melted. The reaction was allowed to proceed without further application of heat until hydrogen chloride was no longer evolved. This required about thirty minutes. The reaction mass was then heated to reflux for ten minutes. The excess thionyl chloride was distilled in vacuo. The expected acid chloride crystallized on cooling, m. p. 130°.

The corresponding amide was prepared from the acid chloride by the general procedure for this reaction. The acid chloride (2 g.) was melted and poured into 20 ml. of conc. ammonium hydroxide. The precipitate was collected by filtration and dried, m. p. 162°. Further purification was not necessary.

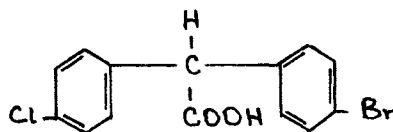
Anal. Calcd. for C₁₄H₁₄ClNO: N, 5.40. Found: N, 5.38.

1,1,1,-Trichloro-2-(4-chlorophenyl)-2-(4-bromophenyl)-
ethane



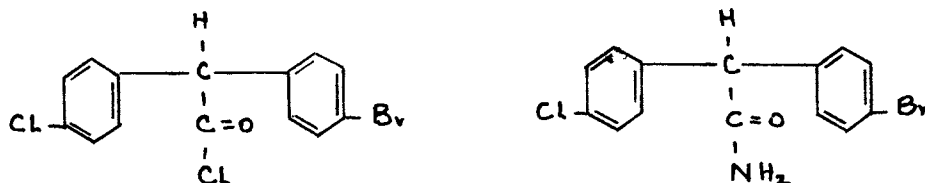
A small, three-necked, round-bottom flask was fitted with a mechanical stirrer, thermometer, and a dropping funnel. Twenty-six grams (0.1 mole) of 1-(4-chlorophenyl)-1-hydroxy-2,2,2-trichloroethane were dissolved in 62 ml. of concentrated sulfuric acid and the solution was placed in the flask. With the temperature at 90°, 31.4 g. (0.2 mole) of bromobenzene were added rapidly, followed by the addition of 50 ml. of concentrated sulfuric acid, dropwise, over a period of one and one-half hours. This mixture was stirred for an additional six and one-half hours. The product mixture was poured over ice and a light brown solid precipitated. The solid was filtered, washed until neutral to litmus paper, and dissolved in alcohol. The alcoholic solution was treated with Norite, filtered and cooled. The crude product was recrystallized from alcohol, filtered, and dried. A yield of 78% was obtained. When pure it melted at 120°. Schneller and Smith reported this compound to melt at 124.5°.³

2-(4-Chlorophenyl)-2-(4-bromophenyl)acetic Acid



A mixture of 400 ml. of diethylene glycol and 55.9 g. (0.14 mole) of 1-(4-chlorophenyl)-1-(4-bromophenyl)-2,2,2-trichloroethane was placed in a 1-l., three-necked flask fitted with a stirrer, reflux condenser and a thermometer. To this mixture was added a solution of 63 g. (1.12 moles) of potassium hydroxide in 35 ml. of water. The mixture was stirred and refluxed for six hours at a temperature of 134-137°. The mixture was then allowed to cool and was poured, with vigorous stirring, into 1000 ml. of cold water, filtered, and washed twice with warm water. The filtrate was boiled gently with 2 g. of Norite for five minutes. The mixture was filtered and acidified to litmus paper with 20% sulfuric acid (approximately 120 ml.) and an additional 30 ml. of the acid was added. The solution was then cooled to 0-5°, the precipitate filtered, washed free of the sulfate ions with water, and dried at 100-110°. A yield of 99% was obtained. When pure the melting point was 48°.

2-(4-Chlorophenyl)-2-(4-bromophenyl)acetyl Chloride and
2-(4-Chlorophenyl)-2-(4-bromophenyl)acetamide



A mixture of 65.1 g. (0.2 mole) of 2-(4-chlorophenyl)-2-(4-bromophenyl)acetic acid and 20 ml. (32 g., 0.27 mole) of thionyl chloride was heated on a steam bath until the acid had melted. The reaction was allowed to proceed without further application of heat until hydrogen chloride was no longer evolved. This required about thirty minutes. The reaction mass was then heated to reflux for ten minutes. The excess thionyl chloride was distilled in vacuo. The expected acid chloride crystallized on cooling, m. p. 57°.

The corresponding amide was prepared from the acid chloride by the general procedure for this reaction. The acid chloride (2 g.) was melted and poured into 20 ml. of concentrated ammonium hydroxide. The precipitate was collected by filtration and dried, m. p. 145°. Further purification was not necessary.

Anal. Calcd. for C₁₄H₁₁ClBrNO: N, 4.27. Found: N, 4.21.

CHAPTER III

DISCUSSION OF RESULTS

The preparation of 1-(4-chloro)-1-hydroxy-2,2,2-trichloroethane (I) proceeded satisfactorily although its purification was not carried out since the compound decomposed when a vacuum distillation was attempted.

The condensation of 1-(4-chloro)-1-hydroxy-2,2,2-trichloroethane with chlorobenzene, bromobenzene, and toluene gave satisfactory yields of DDT, 2-(4-bromophenyl)-2-(4-chlorophenyl)-1,1,1-trichloroethane and 2-(4-chlorophenyl)-2-(4-tolyl)-1,1,1-trichloroethane respectively. However, repeated attempts to condense anisole and thiophene with the substituted ethanol (I) resulted in complete failure.

The hydrolysis of the diaryltrichloroethanes (II) to the corresponding acids (III) gave almost quantitative yields. The one exception was the attempted hydrolysis of 2,2-bis-(2-thienyl)-1,1,1-trichloroethane which gave only a brown mass from which nothing crystalline could be obtained. However, different conditions for the reaction should yield the dithienylacetic acid. The acids, which were obtained by these reactions, were characterized by conversion to the acid chlorides and then to the amides. Both reactions gave satisfactory results.

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