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Some Esters of 2-Trichloro-1-(*p*-chlorophenyl)-ethanol as Potential Insecticides

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Introduction

Since the introduction of DDT, 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane, as a potent contact insecticide with residual characteristics,[2] a number of its structural analogs have been prepared in an effort to obtain other useful insecticides.

The search for compounds which might act as a synergist to or serve as a substitute for DDT is currently stimulated by the recent observations that some insects, notably house flies, are able to develop considerable resistance to the toxic effects of DDT.[3]

DDT is presumed to act as an insecticide through its neurotoxic *p*-chlorophenyl radicals and its lipophilic trichloromethyl group, a combination which reaches a high degree of biological activity in this particular molecule.

In view of the high activity of DDT and the increased solubility of lipoids in solvents having an ester grouping, it appears worthwhile to prepare a series of compounds having a *p*-chlorophenyl radical, a trichloromethyl group, and an ester linkage for biological testing. Additional support comes from the presence of an ester linkage in the pyrethrins,[4,5] in one of the active constituents of "piperonyl cyclohexanone"[6] and in certain lactones,[7] all of which are potent insecticides.

The synthesis of 2-trichloro-1-(*p*-chlorophenyl)-ethanol by the procedure of Howard[8] and its subsequent esterification with appropriate acids provide compounds having these structural features. Moreover, the esters of 2-trichloro-1-(*p*-chlorophenyl)-ethanol with *o*-chlorobenzoic acid and *p*-chlorobenzoic acid bear an isosteric relationship to DDT.[9]

Technical grade *p*-chlorobenzaldehyde (Heyden Chemical Co.) was condensed with dry chloroform in the presence of solid potassium hydroxide to give 2-trichloro-1-(*p*-chlorophenyl)-ethanol in average yields of 25%. Preliminary trituration of the alkali with anhydrous sodium sulfate was advantageous from the standpoint of manipulation. Other modifications, including the carrying out of the reaction at elevated temperatures and the use of other condensing agents, failed to increase the yield of the desired alcohol. Attempts to obtain the 2-trichloro-1-(*p*-chlorophenyl)-ethanol by condensing chlorobenzene and chloral gave none of the desired product or led to the formation of 2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane in low yields depending upon the conditions of the individual reactions.

The hydroxyl group of 2-trichloro-1-(*p*-chlorophenyl)-ethanol was replaced through the use of thionyl chloride in order to obtain the corresponding 1,1,1,2-tetrachloro-2-(*p*-chlorophenyl)-ethane for biological testing.[10]

The esters, listed in Table I, were obtained by the procedures described in the experimental part under Methods I and II. The esters occur as white solids which, in general, could be recrystallized from one of the lower aliphatic alcohols.

2-Trichloro-1-(*p*-chlorophenyl)-ethyl *p*-chlorobenzoate occurred as a colorless crystalline product and in this respect resembled the other esters described here. However, after several recrystallizations from acetone–ethanol (3:2) and from *n*-butanol, this ester continued to melt in the range (145–155°) regardless of whether its melting point was determined on a slowly heated, rapidly heated, or a preheated melting point block. An additional ester, 2-trichloro-1-(*p*-chlorophenyl)-ethyl 2,4-dinitrobenzoate, was also prepared, but the sample obtained by our procedure could not be sufficiently purified for analytical purposes.

Experimental

2-Trichloro-1-(*p*-chlorophenyl)-ethanol.—Five and six-tenths grams of potassium hydroxide (0.1 mole) was well triturated with an equal weight of anhydrous sodium sulfate. This mixture was slowly added in divided portions to a constantly stirred solution of 43 g. of technical grade *p*-chlorobenzaldehyde (0.33 mole) in 40 ml. of dry C.P. grade chloroform (0.5 mole). After standing for several hours, the reaction mixture was treated with 200 ml. of ether and the mixture was filtered. The ether and excess chloroform were distilled from the filtrate, after which it was steam distilled to recover the unreacted *p*-chlorobenzaldehyde. The residue was extracted with ether, and the ether extract was washed with a 5% sodium carbonate solution and dried over sodium sulfate. The ether was removed by distillation, and the 2-trichloro-1-(*p*-chlorophenyl)-ethanol was distilled under reduced pressure, b. p. 185–190° at 25 mm.

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[2] Müller, U. S. Patent 2,329,074.

[3] Wilson and Gahan, *Science*, **107**, 276 (1948).

[4] Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 177-259 (1924).

[5] Staudinger and Ruzicka, *ibid.*, **7**, 377-458 (1924).

[6] Wachs, *Science*, **105**, 530 (1947).

[7] Läuger, Martin and Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

[8] Howard, THIS JOURNAL, **57**, 2317 (1935).

[9] After this work was underway, Barry and Boyer, *Can. J. Research*, **26B**, 511 (1948), reported 1-(4-chlorophenyl)-1-(trichloroacetoxy)-2,2,2-trichloroethane to be one-tenth as active as DDT against the *Drosophila melanogaster* fruit fly, and 1-(4-chlorophenyl)-2,2,2-trichloroethyl methyl succinate to be even less active against this insect. More recently, the monochloro-, dichloro- and trichloroethanol esters of *p*-chloro-, *o*-chloro-, 2,4-dichloro- and 3,4-dichlorobenzoic acids were prepared and found to be inactive when tested as a 5% dust formulation against several species of crawling insects (Woodburn and Sroog, THIS JOURNAL, **71**, 1709 (1949)).

[10] Haller, Bartlett, Drake, Newman, Cristol, Eaker, Hayes, Kilmer, Magerlein, Mueller, Schneider and Wheatley, *ibid.*, **67**, 1601 (1945).

TABLE I

SOME ESTERS OF 2-TRICHLORO-1-(*p*-CHLOROPHENYL)-ETHANOL

Esters 2-Trichloro-1-(*p*-chlorophenyl)-ethyl	Method of prepn.	Solvent used for purif.	Yield %	M. p., °C.	Chlorine, %		Larvae % mort.[b] hours	
					Calcd.	Found	0.5	18
Acetate	I	HAc (60%)	70	123–124.5	46.98	47.00	0	11
Chloroacetate	I	HAc (60%)	57	90.5–91.5	52.71	52.40	0	0
Furoate	II	Ethanol	54	106–107.5	41.52	41.50	3	7
Phenylacetate	I, II	Ethanol	56	62–64	37.57	37.48	21	11
o-Chlorobenzoate	I, II	Ethanol	44	103–104.5	44.54	44.46	0	70
p-Chlorobenzoate	II	Acetone (3) Ethanol (2)	66	145–155[a]	44.54	44.30	21	74
2,4-Dichlorophenoxyacetate	I, II	*n*-Butanol	35	220–222	46.00	45.75	11	0
Benzenesulfonate	II	Ethanol	57	105–106	35.50	35.70	3	11
DDT							96	89

[a] This compound gave every appearance of being pure, but the melting point range remained 145–155° after repeated recrystallizations from acetone–ethanol. [b] These values were obtained from three replications, each including controls, by exposing groups of 4th instar *A. quadrimaculatus* larvae for five-tenths and eighteen hours, respectively, to 200 ml. of water to which had been added 0.1 ml. of a 5% solution of the compound dissolved in cyclohexanone. In the groups exposed for five-tenths hour, the larvae were transferred to fresh water and held for twenty-four hours preparatory to determining mortality. Mortalities were determined at the end of the exposure period in the groups exposed for eighteen hours.

Method I.—To 0.1 mole of 2-trichloro-1-(*p*-chlorophenyl)-ethanol contained in a 100-ml. boiling flask was added 0.12 mole of the selected acid chloride. In some instances, the acid chloride was prepared from the corresponding acid and thionyl chloride after which it was used directly following removal of the excess thionyl chloride. The reaction mixture was refluxed on a water-bath until the evolution of hydrogen chloride ceased. This required from one to two hours. The flask was cooled to effect solidification of the ester after which it was washed with water and then recrystallized from an appropriate solvent.

Method II.—To 0.1 mole of the 2-trichloro-1-(*p*-chlorophenyl)-ethanol contained in a 100-ml. boiling flask was added 0.12 mole of the selected acid chloride. An excess of 15% aqueous sodium hydroxide was added, and the flask was shaken until the ester separated. The solidified ester was filtered with suction, washed with water, and then purified by recrystallization from an appropriate solvent.

Insecticidal Activity.—The esters listed in Table I as well as the parent alcohol, 2-trichloro-1-(*p*-chlorophenyl)-ethanol and the corresponding halogenated hydrocarbon, 1,1,1,2-tetrachloro-2-(*p*-chlorophenyl)-ethane, were tested as contact poisons against mosquito larvae and adult house flies. At a dilution of 1–400,000, two of the compounds, namely, 2-trichloro-1-(*p*-chlorophenyl)-ethyl *o*-chlorobenzoate and the corresponding *p*-chlorobenzoate showed a moderate larvicidal activity in comparison to that of DDT, when tested at an exposure period of eighteen hours. Low rates of mortality were obtained in groups of house flies, especially among the females, held for one hour in contact with 200 mg./sq. ft. deposits of the compounds on glass plates. Both male and female house flies exhibited a rapid and definite but non-fatal paralysis on like exposure to identical deposits of 2-trichloro-1-(*p*-chlorophenyl)-ethanol.

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Summary

Eight esters of 2-trichloro-1-(*p*-chlorophenyl)-ethanol were prepared and tested for their larvicidal activity against the larvae of the *A. quadrimaculatus* mosquito and for their insecticidal activity against the adult house fly, *Musca domestica*. The parent alcohol and all of the esters reported here were inferior to DDT in these tests.

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