Identification of Three Neutral Contaminants in Production Grade 2,4-D

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The structure of a major neutral contaminant in production grade 2,4-D is derived by chemical and spectroscopic data and confirmed by synthesis. Two other neutral impurities are tentatively identified and shown to be isomeric with the major neutral contaminant by combined glc–mass spectroscopy. Evidence is presented to show that these impurities can interfere with the glc analysis of 2,4-D for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin content.

Although the toxicology of pesticides is extensively studied, little research has been devoted to the nature and toxicological significance of trace amounts of impurities in pesticide chemicals. However, the observation (Courtney *et al.*, 1970) that samples of 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) used in a teratogenic study contained significant amounts of the highly toxic compound 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Higginbotham *et al.*, 1968) has led to an increased interest in the nature of impurities in pesticides.

Recently, we had occasion to analyze, by gas–liquid chromatography, the neutral extracts of some samples of production grade 2,4,5-T and 2,4-D (2,4-dichlorophenoxyacetic acid). The glc tracings of the extracts from both pesticides indicated the presence of several neutral contaminants and in the case of the 2,4-D extract three of these impurities had very similar retention times to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. The present paper describes the isolation and characterization of the major of these three impurities and the tentative identification of the other two. Furthermore, this work points out the need for caution on the part of the analyst in interpreting glc data alone when analyzing samples of pesticides for impurities.

EXPERIMENTAL

Materials. All solvents were pesticide grade and used as received. Production grade 2,4-D and the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin were generously supplied by Dow Chemical Company, Midland, Michigan. 2,6-Dichlorophenol, 2,4-dichlorophenol, and methylene iodide were obtained from Aldrich Chemical Company, Eastman Organic Chemicals, and Fisher Scientific, respectively.

Instruments. Mass spectra were obtained with a Hitachi Perkin-Elmer (RMS-4) mass spectrometer coupled with a Perkin-Elmer (Model 990) gas chromatograph, fitted with flame ionization detectors. The stainless steel column, 6-ft × $^1/_8$-in. o.d., was packed with 3% XE-60 on 100–120 mesh Chromosorb W (HP), Chromatographic Specialties Ltd. Operating conditions were: detector and injector temperatures, 220°C; oven temperature, 200°C; carrier gas, helium at a flow rate of 34 ml/min. Nmr spectra were obtained with a Varian A-60A spectrometer in deuterochloroform solution with tetramethylsilane as internal standard. Ultraviolet spectra were obtained with a Unicam model SP 1800 spectrometer. Melting points were determined with an Electrothermal capillary melting point apparatus and are uncorrected. Microanalyses were performed by A. B. Gygli, Microanalysis Laboratories Limited, Toronto, Ontario.

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Chromatography. Baker analyzed reagent silica gel was used for column chromatography. Preparative thin-layer chromatography was performed on plates coated with 0.5 mm silica gel (MN-Silica Gel G/u.v.$_{254}$, Macheney, Nagel & Co.). A mixture of hexane–benzene (4:1) was used as developing solvent. Glc analyses were obtained on several instruments using the columns and conditions listed in Table I.

Extraction of 2,4-D Neutral Impurities. Production grade 2,4-D (1 kg) was extracted by shaking with hexane (1 l.) and filtering through a medium porosity sintered glass funnel. The extraction process was repeated with four additional (1 l.) portions of hexane. A total of 8 kg of 2,4-D was processed in this manner and the combined extracts were evaporated to dryness on a rotary evaporator at 40°C. The residue was taken up in ether (100 ml) and extracted with two 50-ml portions of 10% sodium hydroxide solution, washed with water (50 ml), and the ether layer was dried with anhydrous sodium sulfate. Evaporation of the ether gave the neutral impurities as a pale yellow semi-solid.

Purification of Impurity III. The neutral residue was dissolved in a minimum amount of hexane and chromatographed on a column of silica gel (1.5 cm × 42 cm). Elution with hexane (200 ml) gave a fraction that contained impurity III as the major component as indicated by glc. Preparative tlc of this fraction gave a band (R_f 0.62) which was eluted with ether and shown by glc to contain impurity III with a trace of impurity II. Three recrystallizations of this material from hexane gave pure III as colorless crystals, mp 101–101.5°C: nmr δ 5.76 (s, 2 H), 7.25–7.41 (m, 6 H); uv λ_{max}^{EtOH} 228 nm (ϵ 19,900), 281 (2740), 289 nm (2240); mass spectrum *m/e* 336 (parent ion).

Anal. Calcd. for $C_{13}H_8O_2Cl_4$: C, 46.42; H, 2.38; Cl, 42.26. Found: C, 46.34; H, 2.35; Cl, 41.24.

Synthesis of Bis(2,4-dichlorophenoxy)methane and Bis-(2,6-dichlorophenoxy)methane (3 and 5). The appropriate dichlorophenol (16.3 g, 0.1 mol), anhydrous potassium carbonate (14 g, 0.1 mol), methylene iodide (4 ml, 0.05 mol) and dry acetone (100 ml) were combined and refluxed for 8 hr. The mixture was cooled, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methylene chloride (100 ml), washed with two 75-ml portions of 10% sodium hydroxide solution, one 75-ml portion of water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a pale yellow solid which was recrystallized twice from 95% ethanol to give colorless crystals of **3** and/or **5**. Bis(2,4-dichlorophenoxy)methane, mp 100–102°C [lit. mp 100.4–100.8°C (Miron and Lowy, 1951)]. Mixture melting point with III 101–102°C; nmr δ 5.75 (s, 2 H), 7.25–7.41 (m, 6 H); mass spectrum *m/e* 336 (parent ion). Bis(2,6-dichlorophenoxy)methane, mp 78.5–80°C; nmr δ 5.68 (s, 2 H), 6.85–740 (m, 6 H); mass spectrum *m/e* 336 (parent ion).