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Preparation and Characterization of Chlorinated Dibenzo-*p*-dioxins

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A series of 13 chlorinated dibenzo-*p*-dioxins containing from 1 to 8 chlorine atoms was prepared for use as standards in the development of analytical methodology for the chlorinated dibenzo-*p*-dioxins and for use in toxicological studies. The synthetic pathways to these materials are reviewed and discussed from the standpoint of yield, convenience, and purity of product. The chemical and physical properties of the various chlorinated dibenzo-*p*-dioxins, including their stability, color reactions, infrared, ultraviolet, nuclear magnetic resonance, and phosphorescence spectra, were investigated. The wavelengths associated with the observed phosphorescence and the triplet state lifetime were dependent upon the number of chlorine atoms and their positions on the dibenzo-*p*-dioxin nucleus.

In the fall of 1957, millions of chickens in the Eastern and Midwestern United States died of a disease (Friedman *et al.*, 1959) characterized by excessive fluid in the pericardial sac. The names "chick edema factor" (CEF) and "hydropericardium toxic factor" (HPTF) were therefore applied to the component(s) in the feed responsible for this symptom. Liver and kideny damage was also observed (Schultz, 1968). Similar outbreaks of the disease occurred in 1960 and 1969; a nondistillable fatty material in the feed (possibly a soapstock) was thought to contain the toxic factor (Firestone, 1971).

The acute toxicity of CEF led to research on the isolation and identification of the causative agent. A chlorinated hexahydrophenanthrene was initially suspected (Wootton and Courchene, 1964; Wootton *et al.*, 1962) but X-ray diffraction showed one component to be 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (Cantrell *et al.*, 1969). It was later realized that a whole series of chlorinated dibenzo-*p*-dioxins was present in a wide variety of products. To date the following products have been implicated (Firestone, 1971): food-grade oleic acids and emulsifiers prepared from them, vegetable oil soapstocks, distillation residues from commercial fatty acid manufacture, and chlorophenols and products prepared from them.

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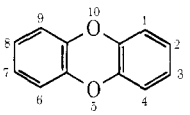
The presence of such highly chlorinated compounds in the food chain is of concern because these compounds are generally fat soluble and nonbiodegradable, tending to concentrate in the food chain, and many of them are acutely toxic and even carcinogenic (Bionetics Research Laboratories, 1967). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, a common contaminant of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), is extremely toxic to a wide variety of animal species (Buu-Hoi *et al.*, 1971a; Farquharson *et al.*, 1957; Higgenbotham *et al.*, 1968; Milnes, 1971; Sparschu *et al.*, 1971) and causes malformations of legs and beaks in the chick embryo (Flick *et al.*, 1965). Its extreme potency as an acnegen is the basis for a sensitive test for the compound (Bauer *et al.*, 1961; Dugois and Colomb, 1957; Jones and Krizek, 1962; Kimmig and Schulz, 1957a,b; Schulz, 1957).

To provide pure standards of the various chlorinated derivatives for use in methods development and toxicology studies, we have synthesized a series of chlorinated dibenzo-*p*-dioxins. This paper presents methods of synthesis, their utility, and physical and chemical properties of the series.

Dibenzo-*p*-dioxin is the name approved by Chemical Abstracts for the basic ring system. Three numbering systems, illustrated below, have been applied to the dibenzo-*p*-dioxin nucleus: I, the Chemical Abstracts system (and the system used by the authors); II, a symmetrical, essentially unambiguous, and easily understood system; and III, a system frequently used in the older literature. Although 75 chlorinated dibenzo-*p*-dioxins are theoretically possible, only

the 2-chloro, 2,7-dichloro, 2,3,7,8-tetrachloro, and the octachlorodibenzo-*p*-dioxin were recorded in the literature at the time this work began. We have reported the synthesis of nine additional chlorinated dibenzo-*p*-dioxins.



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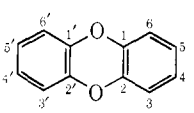

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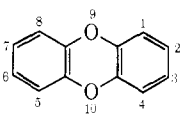


III

EXPERIMENTAL SECTION

Melting points were determined on a Fisher–Johns apparatus and are accurate to within ±1°. Infrared spectral data were obtained with a Perkin-Elmer 621 infrared spectrophotometer and KBr disks. Ultraviolet spectral data were obtained with a Perkin-Elmer Model 202 ultraviolet-visible spectrophotometer. Phosphorescence spectra were obtained with a Perkin-Elmer Model MPF-2A recording spectrofluorometer with phosphorescence attachment. Nmr data were obtained in $CDCl_3$ with a Varian HA-100 spectrometer. Mass spectral data were recorded with an Atlas CH-4B mass spectrometer. Gas chromatographic data were obtained with a Packard Model 7823 gas chromatograph using a hydrogen flame detector. For comparison purposes, all compounds were run on the same day at 172° with 80 ml/min N_2 flow rate and a 6 ft OV-101 column.

Dibenzo-*p*-dioxin. This compound was prepared according to the procedure described by Gilman and Dietrich (1957). The product, obtained in 10% yield, was recrystallized twice from isopropyl alcohol, mp 122–123° [lit. mp 119–122° (Cullinane and Davies, 1936; Cullinane *et al.*, 1934; Gilman and Dietrich, 1957; Tomita, 1945; Tomita *et al.*, 1954)]. A sample prepared by sublimation at 85–90° (1 mm) melted at 122–123°; λ_{max}^{MeOH} 228 (ε 20,500), 290 nm (ε 3700); $\lambda_{max}^{i\text{-oct}}$ 230 (ε 9760), 290 nm (ε 3570); nmr AA'BB' pattern centered at δ 6.81 (35°); glc retention time 1.77 min.

1-Chlorodibenzo-*p*-dioxin. In a 250-ml, single-necked, round-bottomed flask was placed 10.01 g (0.10 mol) of catechol, 11.22 g (0.20 mol) of KOH, 16 (0.088 mol) of 1,2,3-trichlorobenzene, and 100 ml of DMSO. The mixture was heated to reflux under a slow stream of N_2 for 5 hr. On cooling, the dark brown mixture was poured, with stirring, over 1 kg of ice. Filtration through 24-cm fluted filter paper yielded a tan solid which was washed with distilled water until the filtrate was neutral and dried (12.36 g, mp 80–90°, 56.6%). This material was chromatographed over neutral alumina and eluted with benzene to yield a colorless product (mp 103–104°) which was recrystallized twice from MeOH; mp 104.5–105.5°; λ_{max}^{MeOH} 232 (ε 23,960), 291 nm (ε 3500); $\lambda_{max}^{i\text{-oct}}$ 236 (ε 10,500), 291 nm (ε 3060); nmr superposition of ABCD and ABC patterns centered at about δ 6.85 (35°); glc retention time 3.68 min.

Anal. Calcd for $C_{12}H_7O_2Cl$: C, 65.92; H, 3.23. Found: C, 65.72; H, 3.25.

2-Chlorodibenzo-*p*-dioxin. The dipotassium salt of catechol was prepared as a green-brown solid by dissolving 11.01 g (0.1 mol) in 50 ml of H_2O containing 11.22 g (0.2 mol) of KOH. Flash evaporation of the solution yielded the potassium salt, which was dissolved immediately in 200 ml of DMSO in a 500-ml, single-necked flask. After the addition of 36.3 g (0.2 mol) of 1,2,4-trichlorobenzene, the mixture was heated at 175° under N_2 for 15 hr. On cooling, the solution was poured, with stirring, over 1 kg of crushed ice and filtered through 24-cm fluted paper. The grey solid which was recovered was washed well with distilled water and dried (15.25 g, 70.5%, mp 79–85°). Three successive recrystallizations of this material from MeOH yielded a colorless solid: mp 88–89° [lit. mp 87–90° (Gilman and Dietrich, 1957)]; λ_{max}^{MeOH} 231 (ε 23,300), 293 nm (ε 4020); $\lambda_{max}^{i\text{-oct}}$ 234 (ε 11,400), 295 nm (ε 3690); nmr superposition of AA'BB' pattern centered at δ 6.78 on an ABC pattern centered at about δ 6.81 (35°); glc retention time 3.56 min.

Anal. Calcd for $C_{12}H_7O_2Cl$: C, 65.92; H, 3.23. Found: C, 65.88; H, 3.20.

2,7-Dichlorodibenzo-*p*-dioxin. The potassium salt of 2,4-dichlorophenol was prepared by dissolution of the phenol (81.55 g, 0.5 mol) in 200 ml of MeOH containing 28.05 g (0.5 mol) of KOH. The resultant solution was allowed to stand overnight; flash evaporation of the mixture then yielded an oil which was taken up in 50 ml of benzene and decolorized with activated carbon. Addition of 100 ml of hexane precipitated the colorless potassium salt.

The potassium salt of 2,4-dichlorophenol (20 g, 0.1 mol) was heated in the presence of 5 g of copper powder in a vacuum sublimator at 250° and 10 mm pressure for 24 hr. A small amount of product dioxin sublimed onto the cold finger. This material was dissolved in 50 ml of benzene, extracted twice with 10 ml of 10% KOH, washed with 10 ml of H_2O, dried over anhydrous Na_2SO_4, and evaporated to yield a light yellow solid. Two recrystallizations from MeOH yielded colorless crystals; mp 209–210° (lit. mp 201–203° (Gilman and Dietrich, 1957; Julia and Baillarge, 1953), 203–205° (Tomita *et al.*, 1959), 207° (Denivelle *et al.*, 1960; Ueo, 1941); λ_{max}^{MeOH} 235 (ε 24,900), 298 nm (ε 5060); $\lambda_{max}^{i\text{-oct}}$ 236 (ε 11,800), 299 nm (ε 4290); nmr ABC pattern centered at δ 6.82 (60°); glc retention time 7.15 min.

2,8-Dichlorodibenzo-*p*-dioxin. The potassium salt of 2,4,4'-trichloro-2'-hydroxydiphenyl ether (Irgasan DP300, Geigy Industrial Chemicals) was prepared by dissolution of the phenol (28.95 g, 0.1 mol) in 200 ml of benzene. After addition of 5.61 g (0.1 mol) of KOH the mixture was refluxed overnight and the water formed was removed with a Dean–Stark trap. The clear solution which resulted was cooled to precipitate the pure white potassium salt.

The potassium salt (25.9 g, 0.08 mol) was intimately mixed with 5 g of copper powder in a 250-ml single-necked, round-bottomed flask. The mixture was heated at 320° for 4 hr. On cooling, the brown residue was extracted with 250 ml of hot benzene, and the benzene solution was filtered, partially evaporated, and cooled to allow precipitation of 16.78 g (82.6%) of light yellow solid, mp 143–150°. Two recrystallizations from benzene yielded a colorless solid, mp 150.5–151°; λ_{max}^{MeOH} 234 (ε 27,300), 297 nm (ε 5120); $\lambda_{max}^{i\text{-oct}}$ 237 (ε 11,700), 299 nm (ε 4680); nmr ABC pattern centered at about δ 6.80 (60°). Glc indicated a pure compound with a retention time of 7.16 min. However, X-ray diffraction data indicated the presence of a second phase of unknown origin.

Anal. Calcd for $C_{12}H_6O_2Cl_2$: C, 56.95; H, 2.39. Found: C, 57.22; H, 2.52.

2,3-Dichlorodibenzo-*p*-dioxin. The dipotassium salt of catechol was prepared as described for 2-chlorodibenzo-*p*-dioxin (yield 67.5%). Successive recrystallization from MeOH and isooctane yielded a colorless solid, mp 163–164°; λ_{max}^{MeOH} 232 (ε 27,000), 306 nm (ε 3600); $\lambda_{max}^{i\text{-oct}}$ 238 (ε 11,500), 298 nm (ε 3420); nmr AA'BB' pattern centered at δ 6.96 and a singlet at δ 7.02 due to the protons in the 1 and 4 positions (35°); glc retention time 7.54 min.

Anal. Calcd for $C_{12}H_6O_2Cl_2$: C, 56.95; H, 2.39. Found: C, 57.02; H, 2.41.

1,2,4-Trichlorodibenzo-*p*-dioxin. In a 500-ml, three-necked flask fitted with a condenser, N_2 inlet tube, and magnetic stirrer was placed 5.5 g (0.05 mol) of catechol, 13.82 g (0.1 mol) of K_2CO_3, and 100 ml of acetone. The mixture was refluxed 0.5 hr, after which 13.05 g (0.05 mol) of 2,3,5,6-tetrachloronitrobenzene in 100 ml of acetone was added. This mixture was refluxed 2 hr; 100 ml of H_2O was added and the mixture was cooled to ambient temperature. The solid grey precipitate was removed by filtration (9.55 g, 41.4%, mp 125–128°). Two recrystallizations of this material from acetone yielded a colorless product, mp 128–129°; λ_{max}^{MeOH} 239 (ϵ 24,800), 295 nm (ϵ 2200); 247 (ϵ 11,600), 290 nm (ϵ 2290); nmr broad singlet at δ 6.88 due to the four protons of the substituted ring and a sharp singlet at δ 7.00 due to the protons in the 3 position (60°); glc retention time 13.6 min.

Anal. Calcd for $C_{12}H_5O_2Cl$: C, 50.13; H, 1.75. Found: C, 50.24; H, 1.92.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. This material was synthesized as described by Sanderman *et al.* (1957). Five recrystallizations from hot anisole yielded colorless needles, mp 305–306° [lit. mp 320–325° (Sanderman *et al.*, 1957), 298–300° (Milnes, 1971), 295° (Tomita *et al.*, 1959), 300–302° (Dietrich, 1957), 302–304° (Elvidge, 1971)]; nmr singlet at δ 6.97 (66°); glc retention time 32.3 min.

1,3,6,8-Tetrachlorodibenzo-*p*-dioxin. The potassium salt of 2,4,6-trichlorophenol was prepared by dissolving the phenol in water containing an equivalent amount of KOH, followed by filtration and evaporation of the filtrate to dryness on a flash evaporator. The potassium salt (10 g, 0.04 mol) was mixed intimately with 10 g of powdered copper and 10 g of K_2CO_3 and the mixture was heated in a vacuum sublimation apparatus at 300–320° at 10 mm of Hg for 5 hr. The white sublimate that had formed on the cold finger was dissolved in 50 ml of benzene; this solution was extracted with three 10-ml portions of 10% KOH, washed with 10 ml of H_2O, and evaporated to yield a colorless solid (2.03 g, 15.3%). Recrystallization three times from benzene–methanol yielded long colorless needles, mp 219–219.5°; nmr AB pattern with ν_A at δ 6.90 and ν_B at δ 7.02 and J_{AB} = 2.4 Hz (66°); glc retention time 32.3 min.

Anal. Calcd for $C_{12}H_4O_2Cl_4$: C, 44.76; H, 1.25. Found: C, 45.11; H, 1.31.

1,2,3,4-Tetrachlorodibenzo-*p*-dioxin. This compound was prepared as described for 1,2,4-trichlorodibenzo-*p*-dioxin; yield was 59.6%. Two recrystallizations from acetone yielded long colorless needles, mp 189°C, that turned pink on exposure to fluorescent lights: nmr broad singlet centered at δ 6.96 (60°); glc retention time 31.1 min.

Anal. Calcd for $C_{12}H_4O_2Cl_4$: C, 44.76; H, 1.25. Found: C, 44.45; H, 1.27.

1,2,3,4,7-Pentachlorodibenzo-*p*-dioxin. In a 250-ml, single-necked flask fitted with a magnetic stirrer was placed 1.63 g (0.005 mol) of 1,2,3,4-tetrachlorodibenzo-*p*-dioxin, 1 g of $FeCl_3$, 100 ml of $CHCl_3$, and a crystal of I_2. A solution (20 ml) of Cl_2 in CCl_4 (0.5 *M*) was added and the mixture was stirred at room temperature overnight; then it was filtered, washed twice with 20 ml of 20% $NaHSO_3$ and 50 ml of H_2O, and flash evaporated to yield a colorless solid (1.67 g, 94%, mp 180–190°). Recrystallization from benzene–methanol yielded a colorless product, mp 195–196°, >95% purity by glc; nmr ABC pattern centered at about δ 6.96 (65°).

Anal. Calcd for $C_{12}H_3O_2Cl_5$: C, 40.44; H, 0.85. Found: C, 40.21; H, 0.88.

1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin. In a 250-ml, single-necked flask fitted with a magnetic stirrer was placed 2.42 g (0.0075 mol) of 1,2,3,4-tetrachlorodibenzo-*p*-dioxin, 1 g of $FeCl_3$, 100 ml of $CHCl_3$, and a crystal of I_2. A solution (45 ml) of Cl_2 in CCl_4 (0.5 *M*) was added and the mixture was stirred at room temperature for 5 days. The precipitate which formed was removed by filtration and dried (2.33 g, 87.6%, mp 220–225°). Recrystallization of this material twice from chloroform and once from anisole yielded a colorless solid, mp 275°, of >95% purity by glc.

Anal. Calcd for $C_{12}H_2O_2Cl_6$: C, 36.87; H, 0.52. Found: C, 36.55; H, 0.55.

1,2,4,6,7,9-Hexachlorodibenzo-*p*-dioxin. This compound was prepared as described for 1,3,6,8-tetrachlorodibenzo-*p*-dioxin except that the potassium salt was dried under vacuum (1 mm) for 24 hr after the first flash evaporation. Yield was 1.61 g (10.9%) of 1,2,4,6,7,9-hexachlorodibenzo-*p*-dioxin, mp 200–210°. Recrystallization from benzene–methanol three times yielded a colorless solid: mp 238–240°; glc retention time 95.4 min; nmr singlet at δ 7.18 (66°). The product was of 90% purity with a small amount of material whose retention time would indicate a pentachloro derivative.

Anal. Calcd for $C_{12}H_2O_2Cl_6$: C, 36.87; H, 0.52. Found: C, 37.11; H, 0.55.

Octachlorodibenzo-*p*-dioxin. The general procedure described by Kulka (1961) was used to prepare this compound; yield 86%; mp 330° [lit. mp 326° (Denivelle *et al.*, 1960), 318–319° (Tomita *et al.*, 1959), 328–331° (Sanderman *et al.*, 1957), 330–332° (Kulka, 1961), 324° (Denivelle *et al.*, 1959)].

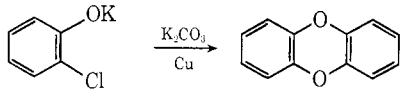
RESULTS

Many procedures for the synthesis of the parent ring system, dibenzo-*p*-dioxin, have been reported (Cullinane and Davies, 1936; Denivelle *et al.*, 1960; Farbenfabriken, 1909; Gilman and Dietrich, 1957; Inubushi *et al.*, 1958; Julia and Baillarge, 1953; Keimatso and Yamaguchi, 1936; Tomita, 1936, 1945; Tomita *et al.*, 1954).

The most common procedure involves the condensation of 2 mol of the alkali metal salt of an *o*-halophenol at high temperature in the presence of a catalyst, usually copper powder or a copper alloy. This is a case of aromatic nucleophilic substitution, and yields are generally low (15–53%). We have routinely used the method of Gilman and Dietrich (1957) to prepare dibenzo-*p*-dioxin itself; *o*-chlorophenol is heated in the presence of potassium carbonate and copper powder, and the black tarry product is refluxed with aqueous potassium hydroxide and extracted with ether. The resulting crude dioxin is purified by chromatography on alumina followed by vacuum sublimation.

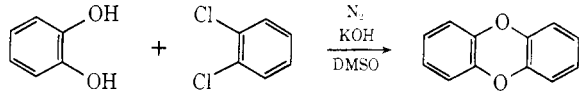
The utility of the method for general use with chlorinated phenols was limited by the formation of complex mixtures of products, presumably because the chlorophenols were not pure but were isomeric mixtures, and because chlorophenols oxidize easily (Musso, 1963). However, several modifications greatly increased the utility of the method. In one modification, use of vacuum sublimation to isolate the product facilitated separation of the chlorodioxin from the other products obtained. The potassium salt of the appropriate chlorophenol was heated at 350° with copper powder or potassium carbonate in a vacuum sublimation apparatus at 10 mm pressure for 12 hr and the dioxin was sublimed onto the cold finger. The sublimate was dissolved in benzene and the solution was washed with 10% KOH and then water, dried (Na_2SO_4), and finally flash evaporated. In every case the crude vacuum sublimate had to be successively recrystal-

Table I. Synthesis of Chlorodioxins from Chlorophenols by Sublimation



Chlorophenol	Chlorodibenzo-*p*-dioxin	Yield, %	Melting point, °C
2,4-Dichloro-	2,7-Dichloro-	10	209–210
2,4,6-Trichloro-	1,3,6,8-Tetrachloro-	15.3	219–220
2,3,5,6-Tetrachloro-	1,2,4,6,7,9-Hexachloro-	10.9	238–240
Pentachloro-	Octachloro-	1.5	330–331

Table II. Synthesis of Chlorodioxins from Chlorobenzenes by Reaction with Catechol

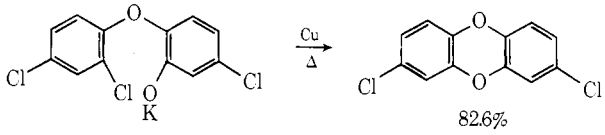


Chlorobenzene	Dioxin	Yield, %	Melting point, °C
1,2,4-Trichloro-	2-Chloro-	70.5	88–89
1,2,3-Trichloro-	1-Chloro-	56.6	104.5–105.5
1,2,4,5-Tetrachloro-	2,3-Dichloro-	67.5	163–164

lized to attain a product of satisfactory purity. The results are shown in Table I.

Although earlier workers had reported that pyrolysis of the silver or sodium salts of trichlorophenol led to formation of polymeric products (Hunter and Seyfried, 1921; Hunter *et al.*, 1916; Tomita *et al.*, 1959), we prepared a 1,3,6,8-tetrachloro derivative that was not polymeric (based upon mass spectral and infrared data) and gave the typical dibenzo-*p*-dioxin nucleus color reaction (Tomita and Ueda, 1963; Tomita *et al.*, 1959).

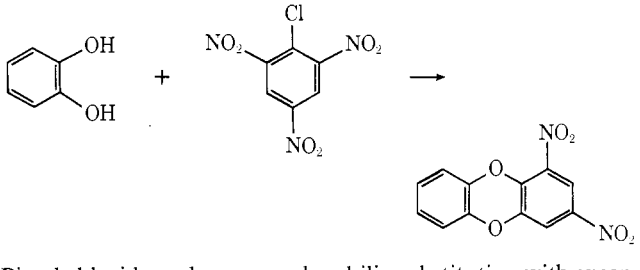
The potassium salt of a substituted diphenyl ether was used to prepare 2,8-dichlorodibenzo-*p*-dioxin, as follows.



82.6%
MP 150-151°

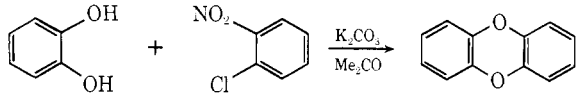
In a second major modification of the Gilman–Dietrich method (1957) the dipotassium salt of catechol reacted with an appropriately substituted chlorobenzene in DMSO (Chandler *et al.*, 1971; Cullinane *et al.*, 1934) (Table II). No dioxin product could be isolated from tetrachlorocatechol monohydrate, however, even under a wide variety of experimental conditions.

Certain nitro-substituted dioxins could be prepared easily by the following reaction scheme (Loudon and McCapra, 1959; Roberts *et al.*, 1935; Tomita, 1945).



Picryl chloride undergoes nucleophilic substitution with exceptional ease, presumably because of the extremely strong –I and –R effects of the three nitro substituents. A steric effect was observed, since the reaction was successful only when nitro groups occupied both positions ortho to the chlorine substituent. Presumably the phenolate anion reacts first to form the corresponding diphenyl ether, followed by a second displacement reaction eliminating the nitro function (Turpin, 1891). This reaction was successfully applied to the condensation of catechol with various nitrohalobenzenes (Table III), but failed when 2,3-dichloronitrobenzene or tetrachlorocatechol was used.

Table III. Synthesis of Nitro-Substituted Dioxins



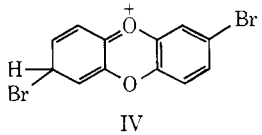
Nitrobenzene	Dioxin	Yield, %	Melting point, °C
Pentachloro-	1,2,3,4-Tetrachloro-	59.6	189
2,3,5,6-Tetrachloro-	1,2,4-Trichloro-	41.4	128–129

The highly toxic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin was prepared in good yield by direct chlorination of dibenzo-*p*-dioxin in chloroform in the presence of ferric chloride and iodine (Sanderman *et al.*, 1957). This synthesis was successful presumably because the product precipitated from the reaction mixture due to low solubility in the chloroform solvent. However, by varying the reaction parameters it was possible to form the octachloro derivative by direct chlorination, but such reactions led to so many difficultly separable products that they were not useful synthetically.

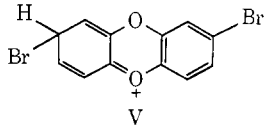
Theoretically one would expect attack by Cl^+ to occur initially at the 2 position, considering the oxygen atom to be an *o,p* director and activator. Thus, the position para to the oxygen is activated toward electrophilic substitution by a strong resonance effect, as is the ortho position; however, the ortho position is deactivated by the I effect of the oxygen more than is the para position. Consequently direct chlorination should lead initially to the 2-chloro isomer.

The position of attack of the second Cl^+ is an intriguing theoretical problem, however. It should enter at the 7 or 8 position, since the chlorinated ring is deactivated. The evidence in the literature, based largely upon the melting point of the isolated product, indicates that the 2,7-dichloro isomer is the major product (Gilman and Dietrich, 1957). The 2,8-dichloro isomer may be more soluble and thus is not isolated. Although the two isomers have not been separated by glc, the structure of the 2,7-dichloro isomer is not in doubt, since the same material has been prepared by three independent synthetic pathways: direct chlorination of dibenzo-*p*-dioxin (Gilman and Dietrich, 1957), pyrolysis of the sodium salt of 2,4-dichlorophenol (Denivelle *et al.*, 1960; Julia and Baillarge, 1953), and from 2,7-diaminodibenzo-*p*-dioxin *via* a Sandmeyer reaction (Ueo, 1941).

The bromination of dibenzo-*p*-dioxin yielded 22% of the 2,8-dibromo isomer but only 7% of the 2,7-dibromo isomer (Gilman and Dietrich, 1957). These results were explained in terms of structures IV and V. The oxonium ion in IV would receive less stabilization from the 2-bromo substituent than the oxonium ion in V.



IV



V

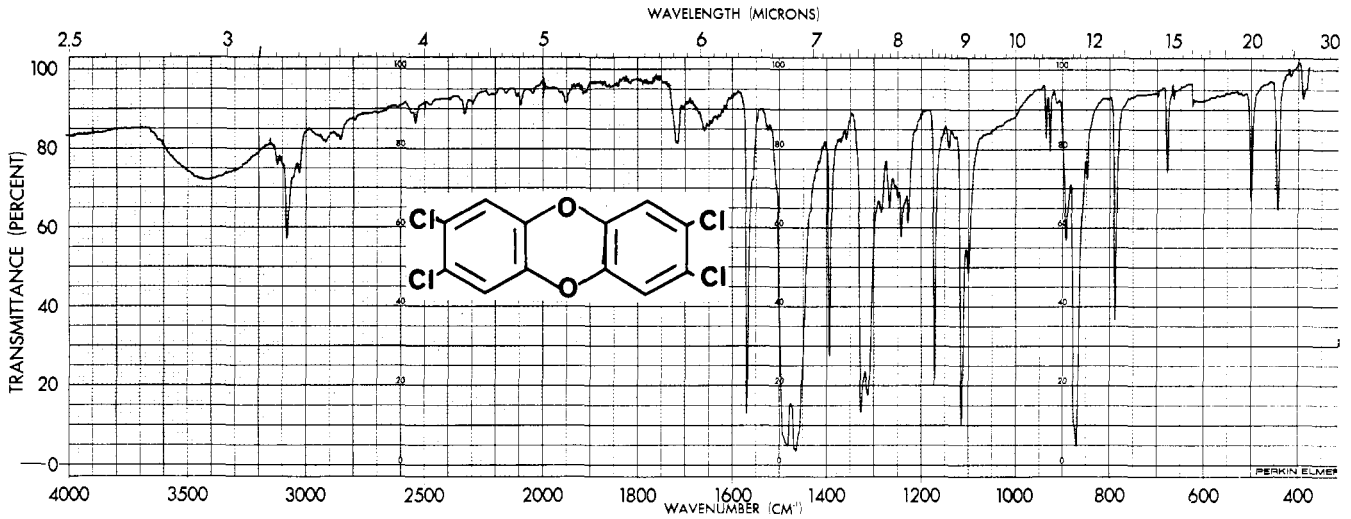
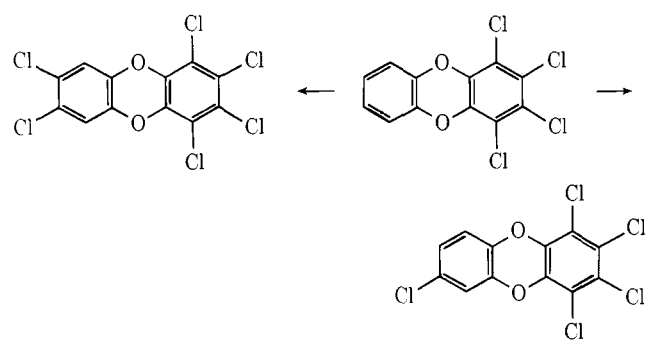


Figure 1. Infrared spectrum of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Aromatic CH stretch: 3122 (uw), 3080 (wm), 3028 (w). C=C skeletal in-plane stretch: 1569 (s), 1493 (s sh), 1473 (vs), 1464 (vs), 1457 (s sh), 1394 (m). =COC= asymmetric stretch: 1327 (s), 1212 (s). CCC trigonal aromatic ring in-plane deformation 1173 (s). Aromatic ring breathing 1115 (s). CH out-of-plane deformation 876 (s sh), 870 (vs). Aromatic CCl stretch 789 (m)

Direct chlorination of 1,2,3,4-tetrachlorodibenzo-*p*-dioxin in the presence of ferric chloride and iodine yielded higher chlorinated products. By carefully controlling the amount of chlorine added, both a pentachloro and a hexachloro isomer were isolated, each in >95% purity (by glc), with the presumed structures shown below. No scrambling of the chlorine atoms of the 1,2,3,4-tetrachloro isomer occurred



under the conditions used, as demonstrated by refluxing the tetrachloro compound in chloroform for 4 days in the presence of ferric chloride and iodine; no rearranged product could be detected by glc.

Direct chlorination of pentachlorophenol in 1,2,4-trichlorobenzene yielded 83% octachlorodibenzo-*p*-dioxin. A free-radical mechanism has been proposed for this reaction, described by Kulka (1961).

MOLECULAR STRUCTURE

The physical properties of these 13 chlorinated dibenzo-*p*-dioxins were carefully investigated. The evidence for the structures of the individual isomers rests primarily upon the method of synthesis, correct elemental analysis, and reasonable infrared, ultraviolet, nuclear magnetic resonance, and mass spectra. In addition, all of the isomers gave the specific blue color reaction characteristic of the dibenzo-*p*-dioxin ring system when treated with concentrated sulfuric acid and an oxidizing agent such as potassium nitrate (Tomita and Ueda, 1963; Tomita *et al.*, 1959). The purity of each isomer was monitored during preparation by glc (flame ionization detector).

Table IV. Ultraviolet Spectral Data for Chlorinated Dibenzo-*p*-dioxins

	$CHCl_3$				
Dibenzo-*p*-dioxin	λ	ϵ	λ	ϵ'	ϵ/ϵ'
Unsubstituted	248	1020	293	3680	0.278
1-Chloro-	248	1320	294	3190	0.414
2-Chloro-	248	1140	299	3700	0.308
2,7-Dichloro-	247	1340	302	4590	0.292
2,8-Dichloro-	247	1180	299	4690	0.252
2,3-Dichloro-	247	1830	304	3190	0.573
1,2,4-Trichloro-	253	5290	294	2250	2.36
1,2,3,4-Tetrachloro-	257	6290	317	2290	2.75
2,3,7,8-Tetrachloro-	248	2970	310	5590	0.532
1,3,6,8-Tetrachloro-	250	5540	305	3440	1.61
1,2,3,4,7-Pentachloro-	259	5920	306	2690	2.20
1,2,3,4,7,8-Hexachloro-	259	5370	316	3660	1.47
1,2,4,6,7,9-Hexachloro-	259	4450	310	1480	3.01
Octachloro-	261	13150	318	2400	5.48

SPECTRAL PROPERTIES

The dibenzo-*p*-dioxin ring system was reported previously to exhibit a characteristically strong absorption band in the 1330–1280 cm^{-1} region, presumably due to the asymmetric stretching of the COC bonds (Narisada, 1959). In this study the position of this absorption band depended upon the total number and position of chlorine substituents (1327 cm^{-1} in the 2,3,7,8-tetrachloro isomer, 1297 cm^{-1} in the 1-chloro derivative, and 1002 cm^{-1} in the octachloro derivative). Aromatic CCl absorption was observed at 789 cm^{-1}; other assignments are found in Figure 1. All of the isomers were distinguished easily from one another by their infrared spectra.

The ultraviolet spectral data for the entire series of chlorinated dibenzo-*p*-dioxins are tabulated in Table IV. Dibenzo-*p*-dioxin absorbed maximally in chloroform at 248 nm (ϵ 1020) and 293 nm (ϵ 3680) (Wratten and Ali, 1967). A bathochromic shift of both absorption bands (Jaffe and Orchin, 1965a) was observed as more and more substituents were added to the dibenzo-*p*-dioxin nucleus. An unusual reversal of peak intensities was observed with chloroform as solvent but not with methanol or isooctane, where the short wavelength absorption band was always much more intense than the long wavelength band.

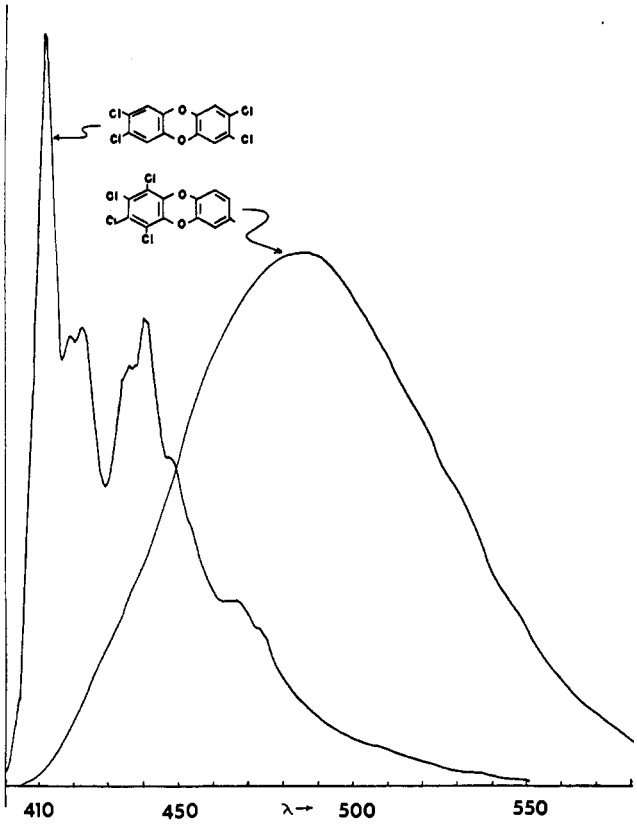


Figure 2. Phosphorescence spectra of 2,3,7,8- and 1,2,3,4-tetrachlorodibenzo-*p*-dioxins

Table V. Phosphorescence Spectral Data for Chlorodibenzo-*p*-dioxins

Dibenzo-*p*-dioxin	Excitation, λ (nm)	Emission bands, λ (nm)
Unsubstituted	294	386, 395,[a] 410, 418, 426,[b] 438
1-Chloro-	296	396, 402,[a] 422, 430[a]
2-Chloro-	295	400,[a] 420
2,7-Dichloro-	300	404,[a] 412, 426, 433, 458, 465
2,8-Dichloro-	304	400,[a] 404,[b] 412, 420, 428, 432, 440, 450, 458
2,3-Dichloro-	312	408, 418, 435[a]
1,2,4-Trichloro-	304	412,[b] 418,[b] 427, 439[a]
1,2,3,4-Tetrachloro-	304	485[a] (very broad)
2,3,7,8-Tetrachloro-	305	411,[a] 418, 422, 436, 440, 448, 468
1,3,6,8-Tetrachloro-	300	410,[a] 418, 433, 438, 465
Octachloro-	310	433,[a] 458, 490

[a] Strongest peak. [b] Peak not resolved.

Intense phosphorescence was observed with dibenzo-*p*-dioxin and all of the chlorinated derivatives. The excitation and emission maxima obtained in EPA (ethanol–isopentane–ether, 2:5:5, Matheson, Coleman and Bell) at 77°K are collected in Table V. Again a bathochromic shift in the absorption maxima was observed as the number of chlorine atoms present increased, presumably due to the admixture of halogen atomic orbitals with the aromatic orbitals, which resulted in increased separation of the singlet and triplet energy levels.

The phosphorescence spectra of the 2,3,7,8-tetrachloro and of the 1,2,3,4-tetrachlorodibenzo-*p*-dioxins are shown in Figure 2. In the symmetrical isomers, *e.g.*, 2,3,7,8-tetrachloro, the emission peaks are relatively narrow and well resolved, indicating singlet–triplet transitions with resolved vibrational levels. Correlations with infrared and raman spectra are currently underway for identification of these phosphorescence substructures. With the highly unsymmetrical isomers, *e.g.*, 1,2,3,4-tetrachloro, however, the emission band was broad and unresolved.

Table VI. Phosphorescence Decay Times of Chlorinated Dibenzo-*p*-dioxins

Symmetrical molecules	Time, sec
Dibenzo-*p*-dioxin	0.54
2,7-Dichloro-	0.29
2,8-Dichloro-	0.22
1,3,6,8-Tetrachloro-	0.25
Octachloro-	0.25
Slightly unsymmetrical molecules	
1-Chloro-	0.22
1,2,3,4,7-Pentachloro-	0.25
Unsymmetrical molecules	
1,2,4-Trichloro-	0.14
1,2,3,4-Tetrachloro-	0.075

Table VII. Mass Spectral Data for Tetrachlorodibenzo-*p*-dioxins

Ion mass	Relative intensity, % 1,3,6,8[a]	2,3,7,8[a]	1,2,3,4[a]
M + (^{35}Cl)	100	100	100
M − (^{35}Cl)	15	15	7
M − (^{35}Cl + CO)	45	35	40
M − 2(^{35}Cl)	5	7	10
M − 2(^{35}Cl + CO)	40	35	50
115	12	20	5
113	10	12	15
110	10	6	0
109	40	40	7
97	45	47	17
99	20	12	10
87	18	10	15
86	5	5	2
85	36	25	7
84	20	22	4
76	2	0	23
75	10	5	23
74	71	68	25
52	2	5	33
51	2	5	25
50	45	50	55

[a] Tetrachlorodibenzo-*p*-dioxin (table prepared by J. N. Damico).

In Table VI the phosphorescence decay times are tabulated. Due to the increase in spin–orbit coupling [the so-called heavy-atom effect (Jaffe and Orchin, 1965b)], the chlorinated dioxins have shorter triplet state lifetimes than does dibenzo-*p*-dioxin itself. A still further reduction in phosphorescence decay time is noted with the heavily unsymmetrical molecules.

The chlorinated dibenzo-*p*-dioxins can be distinguished from the chlorinated dibenzofurans and chlorinated diphenyl ethers (Firestone *et al.*, 1972) by their characteristic mass spectral fragmentation patterns (Firestone *et al.*, 1972), in which the parent ion (M^+) is most intense, but then apparently fragments, losing a chlorine atom ($M^+ - Cl$), and CO [$M - (CO + Cl)$ and $M - 2(CO + Cl)$].

In Table VII are compiled mass spectral data for three isomeric tetrachlorodibenzo-*p*-dioxins. The data show that the characteristic peaks arising from chlorine-containing fragments cannot distinguish between the isomers, since the relative intensities for these fragments are quite similar (Buu-Hoi *et al.*, 1971b). The 1,2,3,4-tetrachloro isomer, however,

differs significantly from the other two isomers in relative intensities (underlined) in the low mass range, and it might be possible to distinguish it from the latter two under static conditions. The inability to distinguish between isomeric chlorinated dibenzo-*p*-dioxins is similar to that observed with tetrachlorobiphenyls (Safe and Hutzinger, 1971).

Mass spectral data in conjunction with the nmr data differentiated among the three tetrachloro isomers. The nmr spectrum of the 1,3,6,8-tetrachloro isomer exhibited an AB pattern with $\nu_A = \delta$ 6.90 and $\nu_B = \delta$ 7.02 and a coupling constant of 2.4 Hz characteristic for meta protons; the 2,3,7,8-tetrachloro isomer exhibited a single peak at δ 6.97.

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