[CONTRIBUTION FROM THE CHEMICAL CORPS., CAMP DETRICK]

BENZOFURAN DERIVATIVES RELATED TO 2,4-DICHLOROPHENOXYACETIC ACID

DAVID STEFANYE AND WILLIAM L. HOWARD

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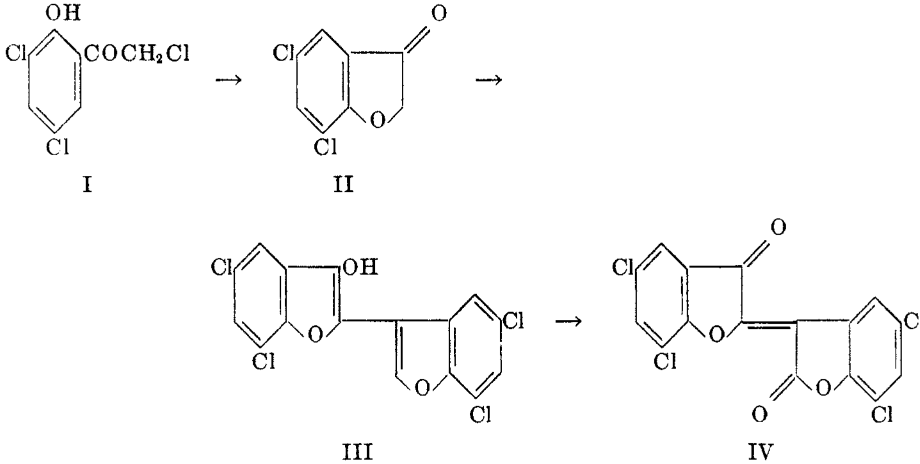
The discovery of the herbicidal properties of 2,4-dichlorophenoxyacetic acid (2,4-D) and its derivatives has stimulated extensive experimentation designed to elucidate the metabolism of these substances in plants. Cyclic structures involving the phenoxyacetyl group have been postulated from time to time as metabolic intermediates. For example, by an extension of the two-point attachment hypothesis of Muir and Hansch (1), Hansch, *et al.* (2) have suggested a structure involving amino and sulfhydryl groups of plant proteins attached at the carboxyl and *ortho* positions in the phenoxyacetyl group. They also mention the possibility of the formation of coumarin types *in vivo*. Recent work in connection with this theory has resulted in the synthesis of 5,7-dichloro-2-oxobenzo-1,4-dioxane (3). Since the coumaranone-3 ring system results from the attachment of the carbonyl of the phenoxyacetyl group to the *ortho* position on the ring, the derivatives of 3(2*H*)-benzofuranone should be of interest in the study of the fate of 2,4-D in the plant. Foremost among these is 5,7-dichloro-3(2*H*)-benzofuranone (II), since it is the cyclization product of 2,4-D.

Thompson (4) mentions the preparation of compound II for plant growth activity tests, but does not describe its synthesis. Kalinowski and Kalinowski (5) sought to synthesize II in three different ways, but were unsuccessful. These authors also state that the Fries rearrangement of 2,4-dichlorophenyl chloroacetate to 2-hydroxy-ω,3,5-trichloroacetophenone (I) could not be effected. During the course of experimentation in this laboratory, the rearrangement was accomplished and is reported herewith, together with the synthesis of II and some of its derivatives.

When the reaction was conducted in nitrobenzene or carbon disulfide, the usual Fries rearrangement solvents, only resinous materials or tars were obtained. The presence of I in these mixtures was demonstrated by the formation of 3-hydroxy-5,5′,7,7′-tetrachloro-2,3′-bibenzofuran (III) on treatment with sodium acetate. III was subsequently shown to be a condensation product of I or II.

Pure I was finally prepared by long heating of 2,4-dichlorophenyl chloroacetate with aluminum chloride in the absence of solvents. Its condensation to II was readily accomplished if air was excluded from the reaction system, although one run without the exclusion of air was successful. If air was present the major product was III which was irreversibly formed. II could also be obtained in small yield by ring closing 2,4-dichlorophenoxyacetyl chloride with aluminum chloride. The above depicted structural formula was assigned to III based on evidence obtained by Fries, *et al.* (6–8). Compound III could be obtained pure, however, only as its acetate. This is not without precedent, since Fries and Pfaffendorf

(7) had similar difficulty in obtaining the unchlorinated homolog in a pure state. Investigation of the chemical behavior of III was difficult, because it proved to be a fairly unstable compound which darkened on exposure to light and was readily oxidized to high-melting, insoluble materials which were difficult to isolate pure. To supplement the chemical evidence available for these products their infrared spectra were determined (Figure 1).



Absence of a carbonyl group in III is indicated by lack of reaction with derivative-forming reagents and no characteristic absorption at 5.5–6μ. Formation of a monoacetate, which could be saponified back to III, and the absorption band at 2.9μ show the presence of a hydroxyl group. When subjected to hydrogenation at room temperature III absorbed two moles of hydrogen per mole, suggesting the presence of two double bonds in the molecule outside the benzene ring, since the reaction went quite easily. Several tautomeric forms may be ascribed to III, but only one was obtained even though this substance was subjected to various recommended treatments (8) such as trituration with acetic acid or heating in acetic acid saturated with dry HCl to displace any equilibrium to the keto form. In the presence of anhydrous HCl, III turned red, but when exposed to the atmosphere it reverted to the original state. This behavior is probably due to the formation of an unstable oxonium chloride. Fries and Pfaffendorf (8) claim the dimethyl homolog is also obtained in only one form.

Oxidation of III was effected with hydrogen peroxide to yield the tetrachloro-oxindirubin, 5,5′,7,7′-tetrachloro-$\Delta^{2,3'}$-bibenzofuran-3(2*H*),2′(3′*H*)-dione (IV). Infrared spectra show a strong double carbonyl band at 5.75μ and 5.85μ, no hydroxyl band at 3μ, and strong evidence of high conjugation at 6.05μ. Comparison of the spectra of II and IV shows that the absorption due to the carbonyl group on the left side of structure IV occurs at 5.85μ. The second carbonyl appears, together with the 6.05μ band, only after treatment with hydrogen peroxide. If a leuco-oxindirubin had been formed, it would have reacted to give an acetate and shown absorption at 3μ; but because of the absence of hydroxyl absorption and the failure of an attempted acylation with boiling acetic anhydride and

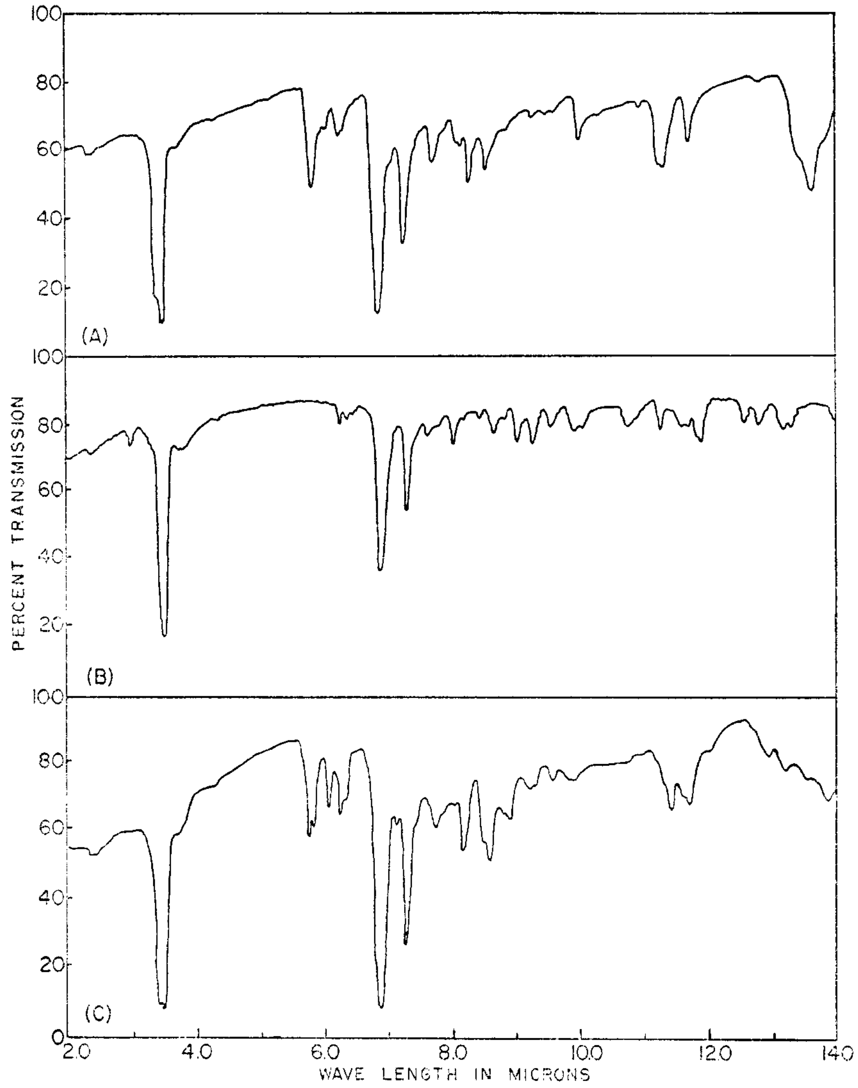


FIG. 1. INFRARED SPECTRA OF (a) 5,7-dichloro-3(2*H*)-benzofuranone, (b) 3-hydroxy-5,5′,7,7′-tetrachloro-2,3′-bibenzofuran, (c) 3,2′-dioxo-5,5′,7,7′-tetrachloro-$\Delta^{2,3'}$-bibenzofuran, in Nujol mull.

sodium acetate, the oxindirubin structure was assigned. Furthermore, if IV was heated with hydrogen peroxide for a long time or treated with bromine in hot acetic acid solution it remained unchanged. These conditions are vigorous, and leuco-oxindirubins are oxidized when subjected to such treatment (6).

EXPERIMENTAL

All melting points were determined with a Fisher-Johns apparatus and are corrected. The chlorine analysis is essentially that described by Vaughan and Nieuwland (9) with an adaptation to provide for the analysis of substances such as 2,4-D which produce tars and colored solutions when degraded with sodium in liquid ammonia. By the substitution of potentiometric titration at *p*H 4–5 their technique was modified to determine halide ion without recourse to adsorption or other end point indicators, which were useless in these colored solutions, or to gravimetric procedures which were time consuming.

Adjustment of the *p*H was necessary, because in more acid solutions the silver electrode was attacked by the nitric acid used causing the voltmeter reading to fluctuate.

ω,3,5-Trichloro-2-hydroxyacetophenone (I). Chloroacetyl chloride (120 g., 1.05 moles) and 2,4-dichlorophenol (163 g., 1.0 mole) were refluxed in a 2-l. distilling flask for 67 hours in an oil-bath maintained at 140–150°. To the resulting 2,4-dichlorophenyl chloroacetate while still hot, powdered anhydrous aluminum chloride (133 g., 1.0 mole) was added and heating was continued at 135–145° for 8 hours. The residue upon cooling solidified to a black mass which was decomposed on the steam-bath with 300 ml. of 20% hydrochloric acid with vigorous evolution of fumes. A black tar soon settled out and upon cooling, this solidified and was separated by filtration to given an oily solid. This material was triturated with ligroin (*d.* 0.67–0.69) to give 150 g. of brown plates. After dissolution in benzene and decolorization with Norit, about 800 ml. of ligroin (*d.* 0.67–0.69) was added to the resulting yellow solution which was allowed to stand overnight. Yellow plates were deposited, filtered, washed with 20–40° pet. ether, and air-dried to give pure I (125 g., 56% yield, m.p. 136–136.8°). This product dissolved in 10% sodium hydroxide to give a red color, gave positive Tollens, haloform, and labile chlorine tests, and dissolved in conc'd sulfuric acid to give a colorless solution. From the mother liquor another 4 g. was obtained, but this material was impure.

Anal. Calc'd for $C_8H_5Cl_3O_2$: C, 40.12; H, 2.11, Cl, 44.50.
Found: C, 40.03; H, 2.14; Cl, 44.65.

5,7-Dichloro-3(2H)-benzofuranone (II). A solution of 12 g. of I in 75 ml. of 95% ethanol was refluxed for 10 minutes in a nitrogen atmosphere. Powdered sodium acetate trihydrate (7 g.) was added all at once to the boiling mixture, washed down the condenser with a little ethanol, and the resulting red solution was refluxed 7 minutes, stoppered, and immediately quenched in an ice-bath, whereupon it solidified. The flask was opened and the contents were transferred into 2 l. of water, filtered, washed with 500 ml. of water, and air-dried to give 11.6 g. of crude material. Upon dissolving in benzene (Norit) and cooling, 0.9 g. of uncharacterized dark amorphous material settled out. The mother liquor was concentrated on the steam-bath in an air stream to a small volume, and upon cooling the coumaranone separated out as yellow needles (5.6 g., 53% yield, m.p. 133–135°). This substance dissolved in conc'd sulfuric acid to give a dark red solution. Upon boiling with sodium hydroxide it gradually turned red. The Tollens test was positive.

Anal. Calc'd for $C_8H_4Cl_2O_2$: C, 47.32; H, 1.99; Cl, 34.98.
Found: C, 47.32; H, 1.99; Cl, 35.00.

This compound was also obtained by ring closure of 2,4-dichlorophenoxyacetyl chloride. A solution of 22 g. of the chloride in 200 g. of carbon disulfide was treated with 20 g. of anhydrous aluminum chloride, which was added over the course of 15 minutes with chilling and shaking. After standing in the cold for 4 hours the resulting red solution was poured into a mixture of 200 ml. of conc'd hydrochloric acid and 500 g. of crushed ice. This liquid then was extracted with benzene and the benzene layer was washed with 10% sodium bicarbonate and twice with water. The material was steam-distilled until the distillate gave only a weak Tollens test. The distillate (4 l.) was extracted with benzene and upon evaporation 1.0 g. of solid was obtained, and recrystallization from ethanol gave II, m.p. 134–135°. A mixture with II obtained from the ring closure with sodium acetate melted at 134–135°.

5,7-Dichloro-3(2H)-benzofuranone oxime. A hydroxylamine derivative was prepared from II. Recrystallization from acetone-water gave an amorphous yellow powder, m.p. 190° with decomposition. Repeated recrystallization from benzene gave fine yellow needles, m.p. 193–194° with decomposition and sublimation.

Anal. Calc'd for $C_8H_5Cl_2NO_2$: N, 6.4; Cl, 32.60.
Found: N, 6.3 (Kjeldahl); Cl, 32.54.

3-Hydroxy-5,5',7,7'-tetrachloro-2,3'-bibenzofuran (III). To a solution of 50 g. of I in 500 ml. of 95% ethanol was added 100 g. of sodium acetate trihydrate as a coarse powder and the resulting mixture was refluxed 30 minutes without excluding air. Upon cooling and pouring the flask contents into 2 l. of cold water a flocculent yellow precipitate formed which upon recrystallization from ethanol gave III as straw-colored needles (36 g., 90% yield, m.p. 192–194° with decomposition, after turning red at 150–160°). From the mother liquor a high-melting resinous material was obtained, which was not characterized. After many recrystallizations from both ethanol and benzene the melting point, analysis, and physical appearance of III were not altered. Upon standing, the surface of these needles gradually darkened. This material dissolved in conc'd sulfuric acid with a red color and was not affected by the action of dilute alkali. Attempts to react III with phenylhydrazine or hydroxylamine failed and starting material was recovered.

Anal. Calc'd for $C_{16}H_6Cl_4O_3$: C, 49.51; H, 1.56; Cl, 36.60; M.W. (Rast), 388.
Found: C, 49.41; H, 2.49; Cl, 33.90; M.W., 377.

Catalytic hydrogenation of II in ethanol in the presence of platinum black and dil. sulfuric acid at 30° and atmospheric pressure resulted in an uptake of 2.3 and 1.7 moles of hydrogen per mole of compound in duplicate determinations.

When II was refluxed in ethanol with sodium acetate for ½ hour and worked up, III was obtained and identified by its melting point and mixture melting point with authentic III obtained directly from I.

3-Acetoxy-5,5',7,7'-tetrachloro-2,3'-bibenzofuran. A mixture of 1.0 g. of III, 25 ml. of acetic anhydride, and 1.0 g. of fused sodium acetate was refluxed for 2½ hours in an oil-bath. Upon cooling a white solid crystallized out, which was filtered, washed well with water, and recrystallized from benzene to give the ester as fine, white, statically charged needles, m.p. 236–238° with decomposition.

Anal. Calc'd for $C_{18}H_8Cl_4O_4$: C, 50.26; H, 1.88; Cl, 33.03.
Found: C, 50.19; H, 1.95; Cl, 33.02.

This material upon saponification with aq.-alc. potassium hydroxide gave a saponification equivalent of 420 (calc'd 430). Upon acidification of the saponification solution past the endpoint, a yellow precipitate formed which upon recrystallization from ethanol melted at 192–194° and did not depress the melting point of III when tested by mixture melting points.

5,5',7,7'-Tetrachloro-$\Delta^{2,3'}$*-bibenzofuran-3(2H),2'(3'H)-dione* (IV). To a solution of 4.5 g. of III in 200 ml. of acetic acid were added 25 ml. of hot water and after a few minutes 15 ml. of 30% hydrogen peroxide, and the mixture was heated on the steam-bath for 15 minutes. A yellow solid soon settled out and was filtered off, washed well with methanol and pet. ether, and then air-dried to give 2.0 g. of IV as a fine yellow powder which carbonized at 337–340° without melting. When a crystallization from ethanol-benzene was attempted, most of the product was converted to a gummy yellow mass, and from the mother liquor IV was again obtained as a yellow powder, washed with methanol and pet. ether, and analyzed. The spectra of crude IV and the analytical sample were practically identical.

Anal. Calc'd for $C_{16}H_4Cl_4O_4$: C, 47.80; H, 1.01; Cl, 35.50.
Found: C, 48.75; H, 1.70; Cl, 35.94.

This material would not react with acetic anhydride and fused sodium acetate. When subjected to prolonged heating with hydrogen peroxide or treated with bromine in hot acetic acid, starting material was quantitatively recovered.

SUMMARY

The Fries rearrangement of 2,4-dichlorophenyl chloroacetate to 2-hydroxy-ω,3,5-trichloroacetophenone and the synthesis of 5,7-dichloro-3(2*H*)-benzouranone and its oxindirubin derivatives have been effected.

FREDERICK, MARYLAND

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