Synthesis of Specific Polychlorinated Dibenzo-p-dioxins[1]

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Received January 19, 1976

A number of tri- through heptachlorodibenzo-p-dioxin (DD) derivatives have been synthesized, most at a high level of purity. The most versatile method for the preparation of specific derivatives in reasonable yield has been found to be the condensation of chloro-substituted catechols with chloro-substituted o-chloronitrobenzenes. Reactivity of the nitrobenzene depends on the position and number of chloro substituents and increases in the order 2,5-di- and 2,4,5-tri- < 2,3,5,6-tetra- < 2,3,4,5-tetra- and pentachloronitrobenzene. 4-Chloro- and 4,5-dichlorocatechol afforded good results in this reaction but 3,4,5-tri- and particularly tetrachlorocatechol proved less satisfactory, undergoing extensive decomposition and giving low yields of desired products. The principal by-products, where there is a chloro substituent adjacent to one located ortho or para to the nitro function of the nitrobenzene, are nitropolychloroDD analogues.

Certain polychlorinated dibenzo-p-dioxins (DD) and some structurally related compounds have been demonstrated to be highly toxic trace contaminants of the environment (see our previous papers for leading references[1-3]). They have caused chloracne and porphyria in industrial workers, and are potent inducers of the enzymes aryl hydrocarbon hydroxylase and δ-aminolevulinic acid synthetase.[4,5]

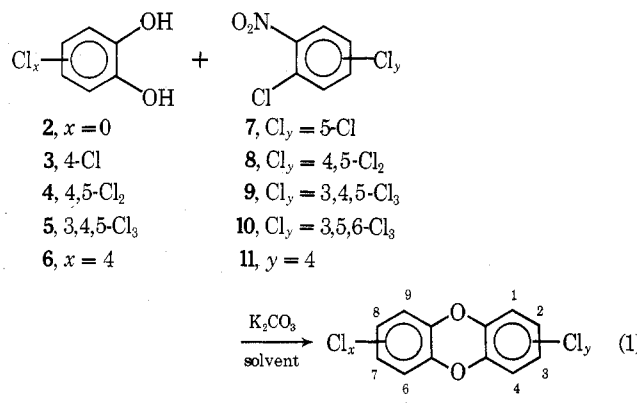
Toxicity is strikingly dependent on the position and number of chloro substituents. Peak toxicity is associated with the 2,3,7,8-tetrachloro homologue (2,3,7,8-tetraCDD), identified as a trace impurity in the herbicide 2,4,5-T and one of the most toxic substances known.[4,5] The 1,2,3,7,8,9-hexachloro analogue (1,2,3,7,8,9-hexaCDD) was identified as the trace contaminant of chicken feed, the so-called chick edema factor, responsible for outbreaks of chick edema disease and the deaths of millions of chickens.[6,7]

In a program aimed at increasing understanding of the nature of the toxicity of these compounds, we have been engaged in the directed synthesis of a number of polychlorinated DD and dibenzofuran (DBF) homologues and isomers at a high level of purity,[1-3] have identified and characterized the products, and made them available for toxicity studies. The present report is concerned with the synthesis of specific polyCDD derivatives.

Chlorinated DD derivatives have generally been prepared by the self-condensation of the alkali metal salts of o-halophenols.[1,2,8,9] Pohland and Yang developed a more attractive approach involving the surprisingly facile condensation of catechol with o-chloropolychloronitrobenzenes in boiling acetone[8] and Kende et al. have condensed catechols at higher temperatures with polychlorobenzenes.[10] These processes have generally afforded mixtures of products and the isolation of pure compounds has proved extremely difficult.[1,2,8-11] It has recently been shown[2,11] that these condensation reactions proceed via Smiles rearrangement, a fact which in large part explains the formation of mixtures of isomeric products in those cases where lack of symmetry makes this possible.

By strategic exploitation of the Smiles rearrangement observed in the phenol condensation process, we were able to isolate both the 1,2,3,6,7,8- and the 1,2,3,7,8,9-hexaCDD (the chick edema factor) isomers in pure form, and identify and characterize the compounds.[2] The occurrence of the rearrangement, however, coupled with the poor yields encountered even under the best conditions made it apparent that this approach had limited value for the synthesis of other desired derivatives. It may be noted that only in a very few instances would the substituents in a phenol be so placed that the product of rearrangement would be identical with that formed by direct self-condensation. A fortuitous example is the synthesis of 2,3,7,8-tetraCDD.[9]

We therefore turned our attention to adaptation of the Pohland and Yang process[8] which, so long as one of the two reactants, either the catechol or the nitrobenzene, has appropriately positioned substituents, the products of rearrangement and of direct condensation will be the same. Thus, the process permits considerably more flexibility (eq 1).



2, $x = 0$
3, 4-Cl
4, 4,5-Cl_2
5, 3,4,5-Cl_3
6, $x = 4$

7, Cl_y = 5-Cl
8, Cl_y = 4,5-Cl_2
9, Cl_y = 3,4,5-Cl_3
10, Cl_y = 3,5,6-Cl_3
11, $y = 4$

1a, 2,3,7-triCDD[12]
b, 1,2,3,7,8-pentaCDD
c, 1,2,4,7,8-pentaCDD
d, 1,2,3,4,7,8-hexaCDD[13]
e, 1,2,3,4,6,7,8-heptaCDD
f, 1,2,3,4,6,7,9-heptaCDD
g, 1,2,3,6,7,9- or 1,2,3,6,8,9-hexaCDD

In this reaction, a chloro substituent ortho to the nitro group and the nitro group of the polychloronitrobenzene are displaced. Pohland and Yang[8] reported the reaction to proceed under surprisingly mild conditions, in boiling acetone, when the reactants were catechol itself (**2**) and either 2,3,5,6-tetrachloro- (**10**) or pentachloronitrobenzene (**11**), but to fail when tetrachlorocatechol (**6**) or 2,3-dichloronitrobenzene were used.

With respect to the catechol, Kende et al.[10] carried out successful condensations of the potassium salts of 4-chloro- (**3**) and 4,5-dichlorocatechol (**4**) with tetrachlorobenzenes and we have had comparable success with the condensation of **3** and **4** with polychloronitrobenzenes. We have also been able to effect similar condensations with 3,4,5-trichlorocatechol (**5**) and with **6**, but these reactants, which have chloro substituent(s) adjacent to a phenolic hydroxyl function, underwent extensive decomposition and afforded extremely poor yields even when precautions were taken to minimize undesired processes.

In regard to the polychloronitrobenzene, we have success-

Table I. GLC Data on Chlorinated Dibenzo-p-dioxins

No.	CDD	RT, min[a,c]	RT, min[a,d]	Rrt[b,c]	Rrt[b,e]
1a	2,3,7-Tri	9.5	2.25	1.00	
1b	1,2,3,7,8-Penta	14		1.72	
1c	1,2,4,7,8-Penta	14	9.1	1.67	
1d	1,2,3,4,7,8-Hexa	14.7		1.9	
1e	1,2,3,4,6,7,8-Hepta	23			7.1
1f	1,2,3,4,6,7,9-Hepta	21.8			6.4
1g	1,2,3,6,7,9- or 1,2,3,6,8,9-Hexa	18.2			3.8
1h	1,2,3,6,7,8-Hexa[f]	18.6	16.3	1.95	
1i	1,2,3,7,8,9-Hexa[f]	18.8	19.6	1.99	
1j	1,2,4,6,7,9-Hexa[g]		10.3	1.91	

[a] Retention time in minutes. [b] Relative retention time vs. dieldrin. [c] Dexsil 300, oven program 150–295 °C at 8 °C/min. [d] Apolar 10C (1%), program 150–230 °C at 10 °C/min. [e] Dexsil 300, isothermal at 270 °C. [f] Gray, Cepa, and Cantrell.[2] [g] Or 1,2,4,6,8,9 isomer depending on whether or not the Smiles rearrangement product was isolated. Prepared by the chlorophenolate condensation process as described by Pohland and Yang;[8] 98% pure (GLC) after chromatography on alumina, elution with hexane containing up to 10% benzene, and recrystallization from chloroform; mp 238–240 °C (lit.[8] mp 238–240 °C); ^{1}H NMR ($CDCl_3$) δ 7.24 (s); ir accords with that reported;[17] mass spectrum *m/e* 396 (9), 394 (38), 392 (94), 390 (100), 388 (53), 331 (8), 329 (17), 327 (26), 325 (18), 266 (10), 264 (23), 262 (19), 196 (17), 195 (16). Anal. Calcd for $C_{12}H_2Cl_6O_2$: C, 36.87; H, 0.52; Cl, 54.52. Found: C, 37.17; H, 0.75; Cl, 54.05.

fully carried out condensations with di- through pentachloronitrobenzenes, those less than tetrachlorinated simply requiring more forcing conditions (e.g., boiling dimethyl sulfoxide or hexamethylphosphoramide[14]). We have found the reactivity of the nitrobenzene to depend on the position and number of chloro substituents and to increase in the order 2,5-dichloro (**7**) and 2,4,5-trichloro (**8**) < **10** < 2,3,4,5-tetrachloro (**9**) and **11**.

The principal by-products of these reactions, where the polychloronitrobenzene bore a chloro substituent in an ortho relationship to a 2- or 4-chloro group, were nitropolyCDD derivatives resulting from displacement of the second, adjacent chloro rather than the nitro function. Amounts of these by-products were increased when more vigorous conditions (e.g., boiling dimethyl sulfoxide) were used or when the attempt was made to increase reactivity of the catechol anion by use of a catalytic amount of a crown ether (18-crown-6) in acetonitrile. In any event, these by-products never formed to an extent sufficient to introduce a serious complication and they were readily removed by recrystallization.

Only one of the catechol condensation reactions reported here, reaction of **5** with **10**, can lead to an isomeric product via Smiles rearrangement. Indeed, in this instance two hexaCDD isomers, the 1,2,3,6,7,9- and the 1,2,3,6,8,9- (**1g**), can be expected regardless of whether or not rearrangement takes place, simply on the basis of the orientation of the reactants prior to condensation. GLC–mass spectral analysis of the crude reaction product did in fact reveal the presence of two hexaCDD isomers but the one having the larger retention time represented only a minor component and was easily removed by recrystallization. The purified product contained only a single hexaCDD isomer (plus about 8% of a pentaCDD homologue arising from dichlorocatechol contamination of the starting material). We are not able to say at this point whether the isolated product is 1,2,3,6,7,9- or 1,2,3,6,8,9-HCDD.

In general, the process of eq 1 afforded reasonable yields of pure polyCDD products. GLC data on these products are given in Table I.

Experimental Section

Caution: Certain of these compounds have been found to be highly toxic and should be handled with extreme care. Work was performed in glove boxes in an isolated toxic laboratory facility. Exhaust air was filtered. All wastes were incinerated. Contact with these compounds can cause chloracne and irreversible liver damage.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were determined with a Varian A-60D spectrometer and are given in parts per million (δ) downfield from tetramethylsilane; ir spectra with a Perkin-Elmer 21 instrument and uv spectra with a Cary 14; GLC–mass spectra were determined at 70 eV with a Hitachi Perkin-Elmer RMU-6D spectrometer linked in tandem to a gas chromatograph. GLC data were obtained with a Varian Aerograph 1200 or 1440 gas chromatograph, hydrogen flame ionization detector, helium flow rate 40 ml/min; 2 m × 0.32 cm columns packed with Dexsil 300, Apolar 10C, or 1% DEGS. Each compound was checked on at least two columns. GLC data are given in Table I. High-pressure liquid chromatography (HPLC) was carried out with a Du Pont 830 instrument. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz., and by Micro-Tech Laboratories, Inc., Skokie, Ill. Analytical data are in accord with structural assignments. Percent purity is based on average GLC response data.

Chlorocatechols. 4-Chlorocatechol (**3**) and 4,5-dichlorocatechol (**4**) were prepared essentially as described by Willstätter and Müller.[15]

Treatment of catechol (**2**) with 1 equiv of sulfuryl chloride in anhydrous ether afforded a 35% yield of **3** indicated by HPLC[16] to be accompanied by a small amount of a contaminant, possibly the 3-chloro isomer.

To an ice-cooled solution maintained under nitrogen of 35.7 g (0.325 mol) of **2** in 150 ml of anhydrous ether was added, dropwise with stirring over a period of 90 min, 58 ml (97 g, 0.72 mol) of sulfuryl chloride. The solution was allowed to warm to room temperature and evaporated under nitrogen to a volume of ca. 75 ml. The crystalline precipitate which formed on standing was collected to afford 22.5 g (39%) of **4** indicated (GLC) to be >97% pure.

The literature method for preparation of 3,4,5-trichlorocatechol (**5**), chlorination of **2** with chlorine,[15] proved difficult to control and gave considerable amounts of tetrachlorocatechol (**6**).[15] The following procedure was therefore adopted.

One molar equivalent of sulfuryl chloride was added to a stirred tetrahydrofuran solution of **4**, maintained under nitrogen at room temperature, and the reaction was followed by GLC. At the point of 40–45% conversion to **5**, significant amounts of **6** began to form and the reaction was stopped. Recrystallization from benzene–hexane yielded 6.5 g of material containing (GLC) 42% of **4** and 58% of **5**. This was twice recrystallized from benzene to give 0.7 g (11% yield) of **5** indicated (GLC) to contain 93% **5** and 7% **4**.

Passing chlorine through a solution of **4** in glacial acetic acid afforded a 21% yield of **6**.

2,3,7-Trichlorodibenzo-p-dioxin (1a). Condensation of **3** with 2,4,5-trichloronitrobenzene (**8**) or of **4** with 2,5-dichloronitrobenzene (**7**) failed to take place to any significant extent when the reactions were carried out in boiling acetone containing potassium carbonate,[8] or even in dimethyl sulfoxide solution at 125 °C. Both condensations proceeded smoothly, however, when the reactants were heated at about 180 °C in either dimethyl sulfoxide or hexamethylphosphoramide.[14]

A solution of 2.75 g (0.015 mol) of 96% pure **4** and 2.06 g (0.01 mol)

of 7 in 25 ml of dimethyl sulfoxide containing 5.5 g of potassium carbonate was heated at reflux for 3.5 h. The reaction mixture was taken up in chloroform and washed with water and dilute alkali. The chloroform solution was concentrated and diluted with methanol to give 0.87 g of precipitate indicated by GLC–mass spectral analysis to consist of 96.7% **1a** and 3.3% of a dichloro homologue. Recrystallization from chloroform–methanol yielded 0.53 g (17%) of **1a:** 99% pure (GLC); mp 162–163 °C;[12] ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 2, $H_1 + H_4$), 6.75–6.95 (m, 3, $H_6 + H_8 + H_9$); ir ($CHCl_3$)[17] 1615, 1575, 1485, 1470, 1375 (aromatic stretch), 1310 (C–O–C stretch), 1295, 1275, 1230, 1110, 1075, 970, 904, 873 (isolated H bend), 860 cm^{-1} (adjacent H bend); uv ($CHCl_3$) 305 nm (ϵ 5200); mass spectrum *m/e* 290 (31), 288 (98), 286 (100), 225 (22), 223 (36), 160 (23), 144 (17), 143 (18).

Anal. Calcd for $C_{12}H_5Cl_3O_2$: C, 50.13; H, 1.75; Cl, 36.99. Found: C, 49.86; H, 1.78; Cl, 37.05.

1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin (1b). An acetone solution of 2.4 g (0.013 mol) of 4 and 2.1 g (0.008 mol) of 2,3,4,5-tetrachloronitrobenzene (**9**) containing 7.2 g of potassium carbonate was heated at reflux for 5.5 h. The reaction mixture was diluted with water and methanol to give 1.6 g of precipitate indicated by GLC–mass spectral analysis to contain 76% of **1b,** the balance being mainly nitropolyCDD materials. Two recrystallizations from chloroform–methanol yielded 0.84 g (29%) of **1b:** 98% pure (GLC); mp 240–241 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (s, 1, H_4), 7.02 (s, 1, H_9), 6.98 (s, 1, H_6); ir ($CHCl_3$)[17] 1565, 1480, 1450, 1380 (aromatic stretch), 1310 (C–O–C stretch), 1115, 955, 915, 875 (isolated CH bend), 838 cm^{-1} (C–Cl stretch); uv ($CHCl_3$) 308 nm (ϵ 6100); mass spectrum *m/e* 360 (21), 358 (70), 356 (100), 354 (67), 295 (12), 293 (24), 291 (18), 230 (11), 228 (11).

Anal. Calcd for $C_{12}H_3Cl_5O_2$: C, 40.44; H, 0.85; Cl, 49.73. Found C, 40.09; H, 0.88; Cl, 49.63.

1,2,4,7,8-Pentachlorodibenzo-*p*-dioxin (1c). Reaction of 4 with 2,3,5,6-tetrachloronitrobenzene (**10**) proceeded only sluggishly in acetone containing potassium carbonate. After 4 h at reflux, 9% of material was obtained indicated by GLC–mass spectral analysis to contain 82% **1c** and 15% nitrotetraCDD products.

A mixture of 5.0 g (0.028 mol) of **4,** 7.9 g (0.03 mol) of **10,** and 7.7 g (0.056 mol) of potassium carbonate in 100 ml of acetone was heated at reflux for 16 h. Workup yielded 0.67 g of **1c** indicated by GLC to be 99% pure and 1.19 g of 97% pure material, combined yield 18.5%. The 99% pure **1c** showed mp 205–206 °C; ^{1}H NMR ($CDCl_3$) δ 7.19 (s, 1, H_3), 7.16 (s, 2, $H_6 + H_9$); ir ($CHCl_3$) 1575, 1560, 1475, 1435, 1407, 1104, 870, 838 cm^{-1}; uv ($CHCl_3$) 307 nm (ϵ 3700); mass spectrum *m/e* 360 (22), 358 (70), 356 (100), 354 (81), 295 (16), 293 (35), 291 (26), 230 (19), 228 (24), 178 (12), 177 (21).

Anal. Calcd for $C_{12}H_3Cl_5O_2$: C, 40.44; H, 0.85; Cl, 49.73. Found: C, 40.74; H, 0.88; Cl, 49.81.

1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin (1d). This compound was prepared in two ways: by condensation of **2** with pentachloronitrobenzene (**11**) followed by chlorination of the product as described by Pohland and Yang,[8] or, at a higher level of purity, by condensation of **4** with **11.** A solution of 0.79 g (4.4 mmol) of **4** and 3.73 g (12.6 mmol) of **11** in 25 ml of acetone containing 2.2 g (15.9 mmol) of anhydrous potassium carbonate was heated at reflux for 5 h. The reaction mixture was poured into water, and the precipitate was collected and washed with hot methanol. The residual solid was recrystallized from chloroform to give 0.75 g (44%) of **1d,** 98% pure (GLC), principal impurities being nitropolyCDD analogues: mp 272.5–273 °C (lit.[8] mp 275 °C); ir accords with that reported;[17] uv ($CHCl_3$) 313 nm (ϵ 4100); mass spectrum *m/e* 396 (12), 394 (32), 392 (80), 390 (100), 388 (45), 329 (14), 327 (24), 325 (15), 266 (7), 264 (14), 262 (12).

Anal. Calcd for $C_{12}H_2Cl_6O_2$: C, 36.87; H, 0.52; Cl, 54.52. Found: C, 36.78; H, 0.47; Cl, 54.40.

1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (1e). Initial efforts to prepare **1e** by monochlorination of **1d** were unsuccessful. We therefore turned to the condensation of **6** with **9.** Care had to be exercised in this condensation to minimize decomposition of the catechol on the one hand, and to avoid products resulting from reaction at the *p*-chloro substituent of the nitrobenzene on the other. Although the process was slow, these objectives were found best achieved by running the reaction in acetone.

A solution of 1.51 g (6.1 mmol) of **6** and 1.36 g (5.2 mmol) of **9** in 40 ml of acetone containing 2.76 g (20 mmol) of anhydrous potassium carbonate was heated at reflux for 90 h. Workup gave 610 mg of material containing (GLC) 30% of **1e.** Recrystallization of this from chloroform, isooctane, and then anisole afforded 114 mg (5%) of **1e,** 93% pure (GLC). This was chromatographed on alumina and eluted with petroleum ether–benzene (85:15) to give 31.7 mg of **1e:** 97% pure (GLC); mass spectrum *m/e* 430 (18), 428 (51), 426 (73), 424 (100), 422 (43), 365 (12), 363 (21), 361 (23), 359 (14).

1,2,3,4,6,7,9-Heptachlorodibenzo-*p*-dioxin (1f). A solution of 0.91 g (3.7 mmol) of **6** and 1.66 g (6.4 mmol) of **10** in 80 ml of acetonitrile containing 2.46 g (17.8 mmol) of potassium carbonate was heated at reflux for 150 h. Addition of a catalytic amount of crown ether (18-crown-6) had no significant beneficial effect on the course of the reaction. The reaction mixture was concentrated to dryness, and the residue was washed with water and twice recrystallized from chloroform to give 5.3 mg of **1f** indicated by GLC–mass spectral analysis to be 91% pure, the major impurities being two hexaCDD isomers.

1,2,3,6,7,9- or 1,2,3,6,8,9-Hexachlorodibenzo-*p*-dioxin (1g). A solution of 0.51 g (2.4 mmol) of **5** and 0.87 g (3.3 mmol) of **10** in 50 ml of acetonitrile containing 1.33 g (9.6 mmol) of anhydrous potassium carbonate and a catalytic amount of 18-crown-6 ether was heated at reflux for 24 h. GLC analysis of the reaction solution showed a major and a small second peak in the hexaCDD region. Workup and recrystallization from chloroform resulted in disappearance of the minor peak and yielded 253 mg (27%) of product indicated by GLC to contain 88% of a single hexaCDD isomer, the major impurities being pentaCDD analogues. It is not possible at this point to make even a tentative structural assignment for **1g:** mass spectrum *m/e* 396 (10), 394 (38), 392 (82), 390 (100), 388 (54), 329 (16), 327 (20), 325 (15), 266 (8), 264 (15), 262 (11), 196 (14), 195 (15), 194 (10).

Acknowledgments. This work was generously supported by FDA Contract 223-73-2197 and, in part, by NCI Contract N01 CP-12338. We thank Drs. A. E. Pohland and D. Firestone for most helpful discussions, Professor A. S. Kende for supplying a preprint of his paper, and Miss A. D. O'Donnell for the GLC–mass spectral analyses.

Registry No—**1a,** 33857-28-2; **1b,** 40321-76-4; **1c,** 58802-08-7; **1d,** 39227-28-6; **1e,** 35822-46-9; **1f,** 58200-70-7; **1g,** 58802-51-0; **1j,** 39227-62-8; **2,** 120-80-9; **3,** 2138-22-9; **4,** 3428-24-8; **5,** 56961-20-7; **6,** 1198-55-6; **7,** 89-61-2; **8,** 89-69-0; **9,** 879-39-0; **10,** 117-18-0; **11,** 82-68-8.

References and Notes

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(12) Kende et al.[10] obtained an impure sample of this compound by condensation of the potassium salt of 4-chlorocatechol with 1,2,4,5-tetrachlorobenzene, mp 153–158 °C.
(13) Pohland and Yang[8] prepared this compound by chlorination of 1,2,3,4-tetraCDD.
(14) Caution: hexamethylphosphoramide has recently been reported to be markedly carcinogenic; see *Chem. Eng. News,* 3 (Feb 2, 1976).
(15) R. Willstätter and H. E. Müller, *Ber.*, **44,** 2182 (1911).
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(17) For analysis of ir spectra of related CDD derivaties see J.-Y. T. Chen, *J. Assoc. Off. Anal. Chem.*, **56,** 962 (1973).