7.64 (10 H, aromatic H, m), 6.44 (H_2, br), 5.47 (H_3, br), 5.11 (H_4, br s), 4.38 (0.6 H, residual H_1, br), 2.98 (3 H, NCH_3, s), 2.59 (3 H, NCH_3, s).

Comments on Standardization of Chemical Shift Values. In our previous report on the ^1H NMR spectra of several of these bicyclic adducts,[2] i.e., **18a** and **18c**, in addition to incorrect assignment of the protons H_1–H_4, we had some difficulty due to nonlinearity of the field on the C-60 HL. This problem was corrected and standards of known chemical shift were used to calibrate all spectra reported here.

Acknowledgments. The authors thank the Special Action Office for Drug Abuse Prevention (SAODAP) and the National Institute on Drug Abuse, Grant DA 00450, for support of this research.

Registry No.—**5a**, 59054-73-8; **10**, 59054-74-9; **11**, 606-37-1; **12**, 2364-46-7; **13**, 59054-75-0; **14**, 28995-89-3; **15a**, 59054-77-2; **15b**, 59054-79-4; **16a**, 59054-81-8; **16b**, 59054-83-0; **17a**, 59054-85-2; **17b**, 59054-87-4; **18a**, 59054-89-6; **18b**, 59054-91-0; **18c**, 59054-88-5; **18d**, 59054-90-9; **19**, 59054-92-1; **20**, 59054-94-3; **21**, 56776-21-7; **22**, 59054-97-6; **23**, 59054-95-4; TNB, 99-35-4; TNB-d_3, 14702-07-9; α-phenoxy-*N*,*N*-dimethylacetamidine, 59054-96-5; α-phenyl-*N*,*N*-dimethylacetamidine, 56776-16-0; 1-deuterio-2,4-dinitronaphthalene, 59054-98-7.

References and Notes

(1) M. J. Strauss, *Acc. Chem. Res.*, **7**, 181 (1974).
(2) R. R. Bard and M. J. Strauss, *J. Am. Chem. Soc.*, **97**, 3789 (1975).
(3) C. F. Bernasconi, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **3**, 33 (1973).
(4) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(5) E. Buncel, A. R. Norris, and K. E. Russell, *Q. Rev., Chem. Soc.*, **22**, 123 (1968).
(6) M. M. Strauss, H. F. Schran, and R. R. Bard, *J. Org. Chem.*, **38**, 3394 (1973).
(7) M. C. Braude, L. S. Harris, E. L. May, J. P. Smith, and J. E. Villarrel, *Adv. Biochem. Psychopharmacol.*, **8**, 1 (1973); N. B. Eddy and E. L. May, "Synthetic Analgesics", B, Pergamon Press, Oxford, 1966.
(8) D. C. Palmer and M. J. Strauss, *Chem. Rev.*, in press.
(9) This antagonist testing was carried out at NIH by Dr. Robert Willette and at the Department of Pharmacology, Medical College of Virginia, by Dr. William Dewey.
(10) W. T. Smith, *J. Am. Chem. Soc.*, **71**, 2855 (1949).
(11) M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Connor, *J. Org. Chem.*, **35**, 383 (1970).
(12) R. R. Bard and M. J. Strauss, unpublished results.
(13) E. R. Ward and C. D. Johnson, *J. Chem. Soc.*, 4314 (1961).
(14) H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 590 (1945).
(15) F. Bell, *J. Chem. Soc.*, 1952 (1952).
(16) H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 533 (1946).
(17) E. Buncel and E. A. Symons, *Can. J. Chem.*, **44**, 771 (1966).
(18) W. T. Smith, *J. Am. Chem. Soc.*, **71**, 2855 (1949).
(19) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 1688 (1947).
(20) The structure for this compound in ref 2 is incorrectly assigned as a 3-benzazocine rather than the correct 2-benzazocine as reported here.

Synthesis of Specific Polychlorinated Dibenzofurans[1]

Allan P. Gray,* Vito M. Dipinto, and I. J. Solomon

Chemistry and Chemical Engineering Research Division, IIT Research Institute, Chicago, Illinois 60616

Received December 23, 1975

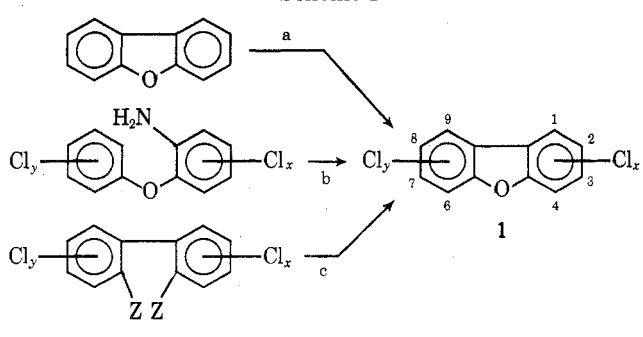
A number of tri- through pentachlorodibenzofuran (DBF) derivatives have been synthesized by specific methods at a high level of purity, characterized, and identified. A diazotization–cyclization process carried out under novel conditions, in tetrachloroethylene with isoamyl nitrite as the diazotizing agent, has been found relatively convenient and general for the synthesis of these compounds. Cyclization of an *o,o'*-biphenol ditosylate derivative under mild conditions has also proved useful. Chlorination of DBF beyond the dichloro stage led to complex mixtures of polychloro derivatives, many of which have been identified. Separation of certain of the isomeric and homologous products has been achieved by high-pressure liquid chromatography.

Certain polychlorinated dibenzofurans (DBF), like their close dibenzo-*p*-dioxin (DD) relatives, have been shown to be extremely toxic trace contaminants of the environment. Along with their DD counterparts, polychlorinated DBF derivatives have been detected and identified in manufactured polychlorophenols[2,3] and thus may appear in a variety of industrial chemical products. The DBF compounds are ubiquitous contaminants of polychlorobiphenyls obtained from various sources[4–7] and the toxicity of these widely used materials has been considered largely attributable to the DBF impurities.[4,8,9] The toxicity of the polychloroDBF derivatives appears to parallel that of their DD analogues, certain of the DBF compounds being extremely toxic to mammals, causing chloracne and producing extensive, irreversible liver damage.[10,11] In the case of the DD derivatives, toxicity is strikingly dependent on the position and number of chloro substituents, peak toxicity being associated with the 2,3,7,8-tetrachloro homologue (2,3,7,8-tetraCDD), one of the most toxic compounds known.[11–13] A corresponding dependence of toxicity on chloro substituents is suspected for the DBF analogues, and in this connection it is noteworthy that 3,4,3',4'-tetrachloroazoxybenzene, a new chemical process intermediate responsible for outbreaks of chloracne and porphyria, has been found to have a parallel toxicologic profile.[11,14]

It is thus of clear importance to investigate these compounds further, to increase understanding of their toxicologic properties and of the relationship of structure to toxicity, and to refine our techniques for detecting and identifying these environmental artifacts. To these ends, we have carried out specific syntheses of a number of polychlorinated DD[1,15,16] and DBF homologues and isomers at a high level of purity, and have identified and characterized the products and made them available for toxicity studies. The present report deals with the synthesis of DBF derivatives.

At the outset, three classic approaches presented themselves as possible routes to desired, polychloroDBF's, viz., (a) electrophilic chlorination of DBF itself; (b) diazotization and cyclization of substituted *o*-phenoxyanilines; and (c) cyclization of substituted *o,o'*-biphenols or their derivatives[17,18] (Scheme I). As Kende et al.[19,20a] have also found in work reported while this investigation was in progress, the most

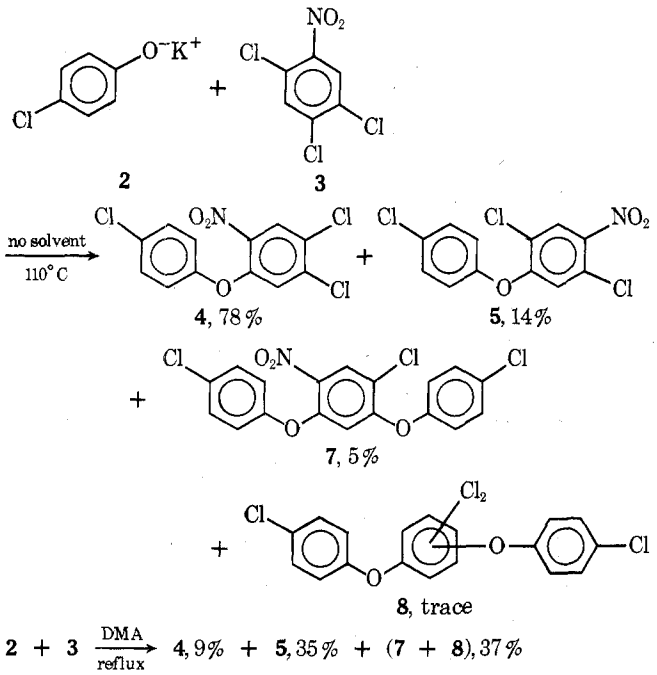
Scheme I



versatile and generally applicable, albeit low-yielding, route to these compounds proved to be via b, the diazotization and cyclization of suitably substituted *o*-phenoxyanilines. We have found, however, that this process is in general difficult to carry out with chlorinated *o*-phenoxyanilines under the usual, aqueous conditions, and have developed a more satisfactory method for effecting the reaction.

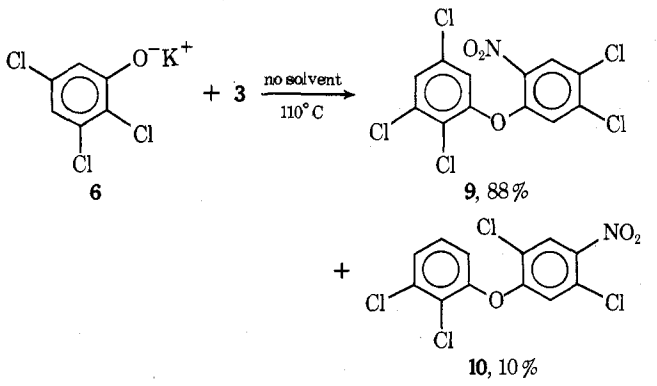
Required starting materials for this process were prepared in two steps: condensation of an appropriately substituted potassium phenolate with an *o*-chloronitrobenzene followed by reduction of the nitro group. It was found best to carry out the first, condensation step, by heating an intimate mixture of the reactants at 110–120 °C in the absence of solvent,[19,20a] under which conditions better yields of cleaner product were obtained. This was particularly true when a *p*-chloro as well as an *o*-chloro substituent was present on the nitrobenzene. In such cases, the desired *o*-nitrodiphenyl ether was the major product in the absence of solvent, whereas in the presence of a high dielectric solvent (dimethyl sulfoxide or dimethylacetamide) the reverse was true, the *p*-nitro isomer predominated and, in addition, more significant amounts of trimeric products formed as a result of displacement of both chloro substituents or (to a minor extent) of one chloro substituent and the nitro group. Thus (Scheme II), in the absence of solvent at 110 °C, potassium *p*-chlorophenolate (**2**) reacted with 2,4,5-trichloronitrobenzene (**3**) to give the ortho-substituted diphenyl ether **4** as the major product whereas in DMA at reflux the para isomer **5** predominated. Similarly, potassium 2,3,5-trichlorophenolate (**6**) reacted primarily at the ortho position of **3** in the absence of solvent at 110 °C but the reverse was true in Me_2SO at the same temperature. The compositions of crude product mixtures were determined by GLC–mass spectrometric analysis. The ortho and para isomeric ether products were distinguished on the basis of their subsequent behavior in the DBF cyclization step. It appears possible to explain these results on the grounds that the close ion pairs likely to be involved in the absence of solvent would favor ortho substitution, whereas a high dielectric solvent would stabilize separated ions, permit greater separation of charge in the transition state, and thereby encourage para substitution.[20b]

Scheme II



$2 + 3 \xrightarrow[\text{reflux}]{\text{DMA}}$ **4**, 9% + **5**, 35% + (**7** + **8**), 37%

+ recovered starting materials



$6 + 3 \xrightarrow[110°\,C]{Me_2SO}$ **9**, 12% + **10**, 42% + trimers + starting materials

(Compositions of crude product mixtures as determined by GLC–mass spectrometric analysis).

Reduction of the chlorinated *o*-nitrodiphenyl ethers to the corresponding phenoxyanilines was carried out uneventfully in good yield with hydrazine and Raney nickel. It was found unnecessary to remove any minor amount of *p*-nitro isomer before reduction since the resultant *p*-phenoxyaniline could not be cyclized to a DBF derivative.

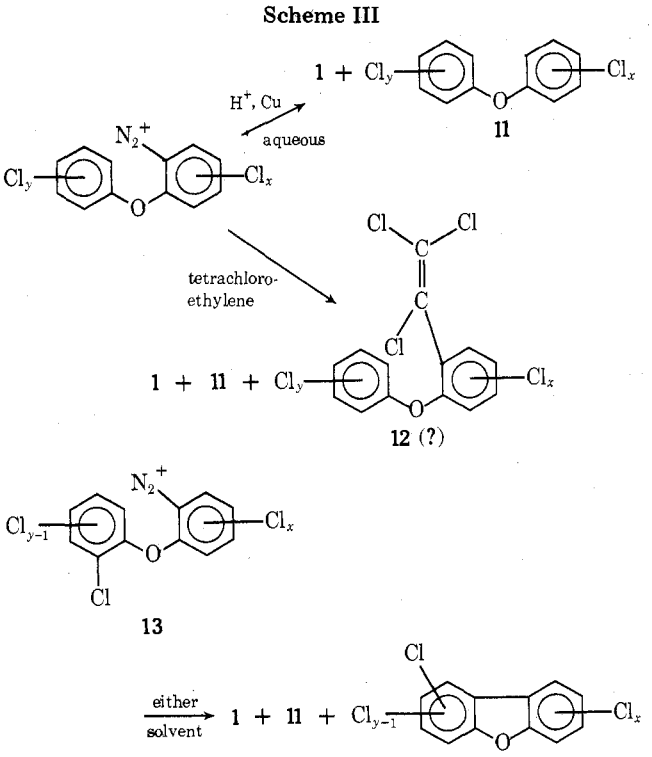
Polychloro-*o*-phenoxyanilines in general proved to be essentially nonbasic and very poorly soluble. These attributes generally precluded carrying out the diazotizations in aqueous mineral acids. The compounds could be diazotized in aqueous acetic acid but even here solubilities of the order of 1 g or less per liter of 75–80% acetic acid made the process most inconvenient, particularly since the resultant solution of the diazonium salt had then to be poured into boiling 1 N sulfuric acid containing a copper catalyst. We therefore sought an organic medium in which diazotization could be effected by means of isoamyl nitrite, with minimal intervention of side reactions of the diazonium salt with the solvent. Benzene could not serve as the solvent since it would be expected to react preferentially with the diazonium salt.[21] A number of solvents were evaluated on a test tube scale, by treating solutions of a small amount of *o*-phenoxyaniline, viz., 2-(*p*-chlorophenoxy)-4,5-dichloroaniline or 2-(3,4-dichlorophenoxy)-5-chloroaniline, with isoamyl nitrite, heating until gas evolution ceased, and then analyzing the reaction solutions by GLC and mass spectrometry. The results obtained with various solvents were as follows. Carbon tetrachloride afforded low yields of triCDBF and large amounts of tri- and tetrachlorodiphenyl ethers as well as other products indicative of interfering reactions with solvent; aliphatic solvents (*n*-heptane, tetrahydrofuran, *tert*-butyl alcohol, glacial acetic acid, trifluoroacetic acid) gave 0–20% triCDBF and up to 80% trichlorodiphenyl ethers, suggesting solvent-mediated reductive cleavage of the diazonium salt; basic solvents (pyridine, acetonitrile) largely yielded recovered starting aniline, suggesting reaction of the solvent with the isoamyl nitrite; nitrobenzene gave a complex mixture of unidentified products; tetrachloroethylene afforded the most promising results, yielding ca. 50% of triCDBF and lesser amounts of trichlorodiphenyl ether.

Tetrachloroethylene has thus far proved to be the solvent of choice for the reaction. In this solvent with isoamyl nitrite as the diazotizing agent, the diazotization and cyclization processes could be conveniently carried out in one pot, simply by heating solutions of the reactants at concentrations of the order of 1–2 g of aniline per 100 ml for 5–6 h at 80 °C.

The DBF usually, but not always, was the primary product by either procedure representing 40–50% of the crude material. Largely owing to losses suffered during purification, however, isolated yields of DBF products were very low (ca. 5%) with either the aqueous acetic acid or tetrachloroethylene procedure. Surprisingly, the principal by-product (30–40%

of the crude mixture) was the corresponding diphenyl ether resulting from reduction of the diazonium salt rather than, at least in the case of the aqueous medium, the expected *o*-phenoxyphenol. Quite to the contrary, no evidence for the formation of phenolic by-products could be obtained. Diphenyl ether products could generally be removed by column chromatography. A minor by-product, representing ca. 5% of the crude reaction product from the aqueous acetic acid procedure or up to 10% in tetrachloroethylene, observed in those instances where only one of the ortho positions on the phenoxy substituent of the aniline was open and the other bore a chloro substituent, was an isomer of the expected polychloroDBF. Isomer formation may result from attack of the phenyl cation at the chlorine-bearing ring position, forcing migration of the chloro substituent. Although the isomers were not isolated and their structures were not determined, their identity as polychloroDBF isomers was established by GLC–mass spectrometric analysis. Direct GLC comparison did indicate that the isomeric DBF's produced in the formation of the two pentaCDBF derivatives, **1d** and **1e**, were different from each other and from the isolated DBF products. Analysis of ^{1}H NMR spectra permits us to be confident that the isolated, major DBF products were the expected isomers derived from direct cyclization without rearrangement. A second minor by-product, occurring only in the tetrachloroethylene medium and representing 10–20% of the crude reaction product from this medium, was identified by GLC–mass spectral analysis as a trichloroethenyl derivative of the chlorinated diphenyl ether, tentatively formulated as **12**, and presumably resulted from attack of the phenyl cation on the solvent. These results are illustrated in Scheme III.

Scheme III

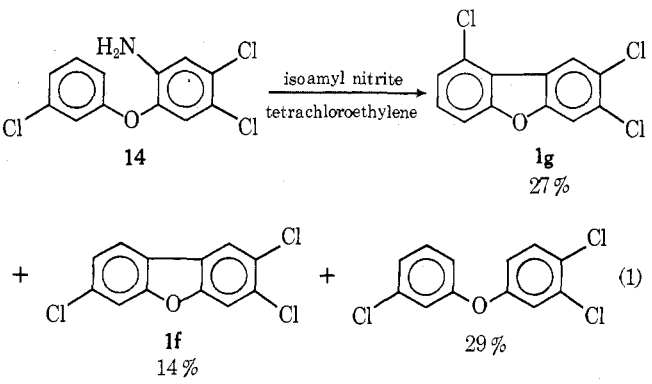


PolyCDBF's prepared according to Scheme III:

1a, 2,3,8-tri[24]
b, 2,4,6-tri
c, 2,3,6,8-tetra[24]
d, 1,2,4,7,8-penta
e, 1,3,4,7,8-penta

It may be noted that generalizations enunciated earlier with respect to the effect of the position of a single substituent on the course of the cyclization, namely that no direct ring closure to a 1-monosubstituted DBF had been successful[17] and that to form a 4-substituted DBF, the substituent must be attached to the aniline rather than the phenoxy nucleus,[17,22] do not apply when several chloro substituents are present. Thus, **1b** was prepared from 2-(2,4-dichlorophenoxy)-3-chloroaniline and **1c** from 2-(2,4-dichlorophenoxy)-4,5-dichloroaniline. The 1-substituted compounds, **1d** and **1e**, were prepared from 2-(2,3,5-trichlorophenoxy)- and 2-(2,4,5-trichlorophenoxy)-4,5-dichloroaniline, respectively.

In this connection, it is significant that an attempt to prepare 2,3,7-triCDBF (**1f**) by cyclization of 2-(*m*-chlorophenoxy)-4,5-dichloroaniline (**14**) afforded predominantly what is presumed to be the 1-substituted isomer, 2,3,9-triCDBF (**1g**) (eq 1). The composition of the crude product mixture was determined by GLC; **1f** was identified by spiking with material



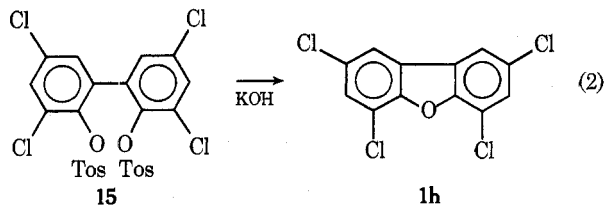
+ 8% trichloroethenyl derivative

prepared by monochlorination of 3,7-diCDBF (vide infra). A small amount of **1g** was isolated by column chromatography; the structural assignment was supported by its ^{1}H NMR spectrum which showed a singlet for the deshielded H$_1$ proton at δ 8.5.

2,4,6,8-TetraCDBF (**1h**)[25] was prepared via route c, cyclization of an *o,o'*-biphenol derivative, since the requisite 2,3,5-trichloronitrobenzene was not readily available for use in route b and since chlorination of **1b** gave a complex mixture of products (vide infra). Although *o,o'*-biphenol itself, simply on being heated, with or without the aid of an acid dehydrating agent (e.g., phosphorus pentoxide, zinc chloride), is cyclized to DBF in excellent yield,[17,18,23] 4,6,4',6'-tetrachloro-2,2'-biphenol proved to be refractory. Subjection of the tetrachlorobiphenol, prepared by chlorination of biphenol with sulfuryl chloride[26] or chlorine, to various acid reagents including zinc chloride and phosphorus pentoxide gave largely recovered starting material under relatively mild conditions or, under more drastic conditions, large amounts of decomposition products accompanied by small amounts of **1h**, which was indicated to be present in the crude reaction mixtures by GLC but which could not be isolated.

Since 2,2'-diacetoxybiphenyls, so long as they bear at least two nitro substituents ortho and/or para to the acetoxy functions (bromo substituents can be present but cannot serve in place of nitro), are readily converted to DBF derivatives by heating under basic conditions in admixture with barium carbonate,[27] it appeared possible that by use of a better leaving group such as tosylate a similar cyclization of the tetrachlorobiphenol could be effected. This has indeed proved to be the case. Treatment of the ditosylate (**15**) with potassium hydroxide, preferably in dimethylacetamide solution under surprisingly mild conditions at 105–110 °C, afforded **1h** in reasonable yield (eq 2).

2,3,7,8-TCDBF (**1i**) was prepared essentially as described by Kende et al.[19,20] from benzidine-2,2'-disulfonic acid following a reaction sequence based on route c.

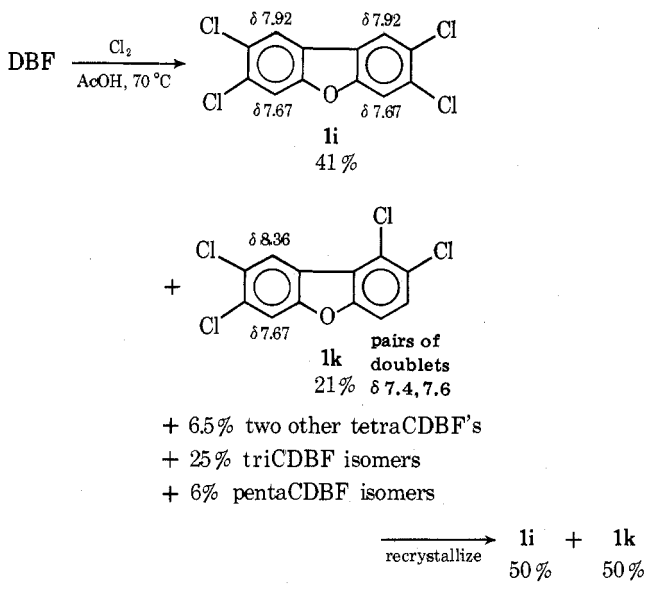


15 1h (2)

Route a proved to be of little value for the preparation of discrete polychloroDBF derivatives. As might have been expected based on its behavior in other electrophilic substitution reactions,[17,18,28,29] chlorination of DBF beyond the 2,8-dichloro stage led to complex mixtures of products. Whether chlorination was carried out in glacial acetic acid or a chlorocarbon solvent with or without ferric chloride plus iodine catalyst, reaction first led cleanly to 2,8-diCDBF (**1j**) and then to mixtures of isomers of more highly chlorinated products.

Chlorination of DBF in glacial acetic acid at 70 °C and stopping reaction when products of tetrachlorination predominated afforded a crude product mixture with the composition shown in Scheme IV determined by GLC–mass

Scheme IV

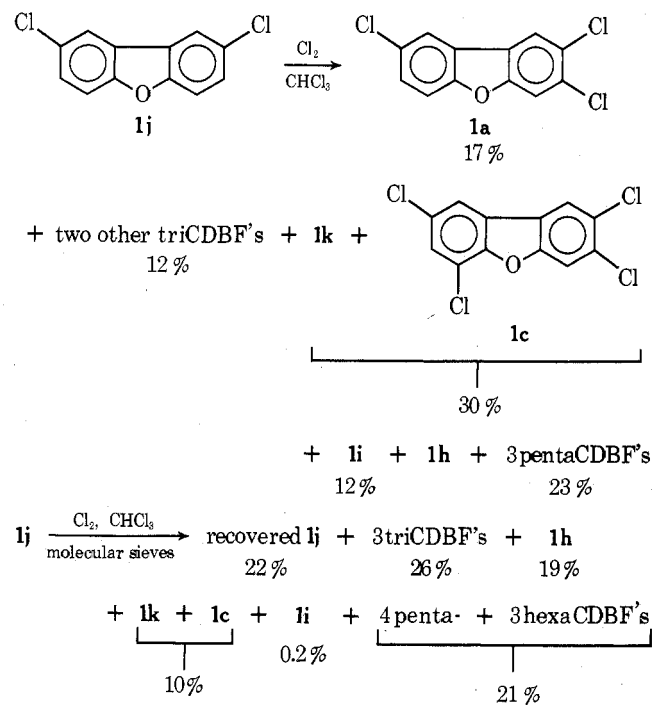


spectrometric analysis. Recrystallization afforded a 1:1 mixture of **1i** and 1,2,7,8-tetraCDBF (**1k**), characterized by analysis of the ^{1}H NMR spectrum. Separation of the two isomers has been accomplished by high-pressure liquid chromatography (HPLC). The formation of so much **1k**, which requires substitution at the 1 position, was quite unexpected based on earlier experience.[17,18,28,29]

Chlorination of **1j** in chloroform containing catalytic amounts of ferric chloride and iodine again to the tetrachloro level afforded a product mixture, the composition of which as determined by GLC–mass spectral analysis and comparison with products synthesized by alternate routes is shown in Scheme V. A recent report of the selective halogenation of alkylbenzenes adsorbed on molecular sieves[30] made it of interest to see if selective chlorination could be similarly achieved. Adsorption of **1j** on molecular sieves did indeed modify the outcome of the chlorination but, as can be seen (Scheme V), in no way improved selectivity. It is most notable that introduction of molecular sieves resulted in the formation of significantly more **1h** (all substituents ortho or para to the ether oxygen) and only a trace of **1i**.

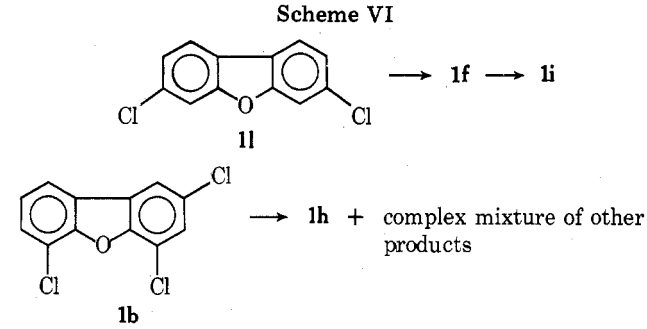
Since chlorination of DBF first goes preferentially to the 2,8 positions (para to the oxygen), it is not surprising that, as reported,[19,20] chlorination of 3,7-diCDBF (**1l**) gives predom-

Scheme V



inantly **1i** (Scheme VI). The process could not be stopped cleanly at the monochlorinated stage and, although **1f** was

Scheme VI



formed by this means, it proved difficult to purify. Isolation of **1f** was finally accomplished by HPLC. In the light of these observations, it appeared reasonable to expect primary introduction of a chloro substituent at the 8 position of **1b** and the clean formation of **1h**. Chlorination of **1b** in either chloroform or acetic acid, however, led to complex mixtures of products containing no more than 20–30% **1h**. The behavior of **1b** is in sharp contrast to that of corresponding nitro analogues; thus, nitration of 4,6-dinitroDBF affords an excellent yield of 2,4,6-trinitroDBF which in turn on further nitration overwhelmingly yields the 2,4,6,8-tetranitro derivative.[28] Explanation would appear to lie in the fact that nitro is a meta-directing substituent which reinforces the influence of the ether oxygen when placed in the 2, 4, and 6 positions, whereas chloro is an ortho-directing substituent which reinforces the influence of the ring oxygen when in the 3 and 7 positions but which counters this influence in the 2, 4, and 6 positions.

GLC data on polyCDBF derivatives are given in Table I. It may be noted that chloro substitution ortho to the ring oxygen, that is in the 4 and 6 positions, tends to decrease retention time.

In sum, use of tetrachloroethylene as a reaction medium and isoamyl nitrite as the diazotizing agent has made the diazotization and cyclization of chlorinated *o*-phenoxyanilines a reasonably convenient and general, if still low-yielding, route to specific chlorinated DBF derivatives.

Table I. GLC Data on Chlorinated Dibenzofurans

No.	CDBF	RT, min[a]	R_{RT}[b]	R_{RT}[c]
1a	2,3,8-Tri	4.5	0.92	1.00
1b	2,4,6-Tri	4.3	0.87	0.88
1c	2,3,6,8-Tetra	7.3	1.52	1.47
1d	1,2,4,7,8-Penta	11.6	2.4	1.66
1e	1,3,4,7,8-Penta	12.0	2.5	1.51
1f	2,3,7-Tri	4.7	0.91	0.92
1g	2,3,9-Tri	4.3	0.87	0.65
1h	2,4,6,8-Tetra	6.0	1.35	1.22
1i	2,3,7,8-Tetra	8.2	1.75	1.83
1k	1,2,7,8-Tetra	7.5	1.59	1.27

[a] Retention time in minutes, Dexsil 300 isothermal at 250 °C. [b] Relative retention time vs. dieldrin; Dexsil 300, isothermal at 250 °C. [c] Relative retention time vs. dieldrin, 1% Apolar 10C, isothermal at 200 °C.

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 averaged GLC response data.

2,3,8-Trichlorodibenzofuran (1a). Heating an intimate mixture of 36.7 g (0.22 mol) of the dry potassium salt of *p*-chlorophenol (**2**) and 49.7 g (0.22 mol) of 2,4,5-trichloronitrobenzene (**3**) at 105–110 °C (bath temperature) for 18 h gave, after workup, 32% of material indicated by GLC to consist of 78% **4**, 14% **5**, 2.7% recovered **3**, and 5.5% **7** plus **8**.

Treatment of 20.0 g (0.063 mol) of the crude product with 11.8 g (0.2 mol) of hydrazine hydrate (85%) in boiling ethanol containing a catalytic amount of Raney Ni[32] afforded, after workup, 8.6 g (47%) of material containing (GLC) 87% of 2-(*p*-chlorophenoxy)-4,5-dichloroaniline and 4.6% of the isomeric aniline.

The crude aniline, 6.9 g, was extracted with approximately 8 l. of 80% acetic acid, and the resultant solution in 1-l. portions was cooled in an ice bath and treated with an aqueous solution of sodium nitrite. The solution of the diazonium salt was then poured in portions into boiling 1 N sulfuric acid containing a catalytic amount of copper[33] and the reaction mixture was boiled for 2.5 h, cooled, and extracted with chloroform. Drying and removal of the chloroform and recrystallization of the combined residues from isooctane afforded orange-red material which was chromatographed on alumina[34] and eluted with hexane–benzene (95:5). Recrystallization of the chromatographed product from chloroform yielded 289 mg (4.5%) of **1a**, colorless crystals, 99.4% pure (GLC), impurities being 0.2% diphenyl ether and 0.4% trimeric material: mp 189–191 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1, H_1), 7.68 (s, 1, H_4), 7.84 (t, 1, J = 1.25 Hz, H_9), 7.48 (d, 2, J = 1.4 Hz, H_6 + H_7); ir ($CHCl_3$)[31] 1606, 1472, 1455, 1392 (aromatic), 1104 (C–O–C), 872 (isolated CH bend), 857 (adjacent CH), 814 cm^{-1} (C–Cl); uv ($CHCl_3$) 256 nm (ϵ 33 000), 302 (29 000), 313 (21 000); mass spectrum *m/e* 274 (28), 272 (80), 270 (100), 209 (15), 207 (23), 137 (14), 136 (10), 135 (11).

Anal. Calcd for $C_{12}H_5Cl_3O$: C, 53.08; H, 1.86. Found: C, 53.04; H, 1.97.

1a was also prepared in similar yield from the phenoxyaniline by the isoamyl nitrite–tetrachloroethylene procedure described in the following example.

1,2,4,7,8-Pentachlorodibenzofuran (1d). An intimate mixture of 9.4 g (0.04 mol) of potassium 2,4,5-trichlorophenolate and 9.1 g (0.04 mol) of **3** was heated for 18 h at 105–110 °C (bath temperature). Two recrystallizations of the crude product from methanol yielded 8.57 g (55%) of 2-(2,4,5-trichlorophenoxy)-4,5-dichloronitrobenzene indicated to be 92% pure by GLC. Treatment of the nitro compound, 8.57 g (0.022 mol), with hydrazine and Raney nickel[32] in boiling 95% ethanol yielded 4.75 g (60%) of 2-(2,4,5-trichlorophenoxy)-4,5-dichloroaniline, 92% pure by GLC.

A solution of 4.75 g (0.013 mol) of the aniline and 2.42 g (0.021 mol) of isoamyl nitrite (commercial or freshly prepared material was equally satisfactory) in 250 ml of tetrachloroethylene was heated to the point at which vigorous gas evolution began. The heat was removed and, after the vigorous gas evolution had subsided (in about 5 min), the reaction mixture was heated at 80 °C (bath temperature) for 6 h during which slow gas evolution continued. Prolonged heating at higher temperatures gave large amounts of resinous materials. At lower temperatures, the reaction proceeded too slowly. The final reaction mixture was indicated by GLC–mass spectral analysis to contain 35% of **1d**, 12% of an isomeric pentaCDBF, 30% of pentachlorodiphenyl ether isomers, and 13% of a presumed pentachloro(trichloroethenyl)diphenyl ether derivative resulting from reaction with the solvent. The reaction mixture was evaporated to dryness in vacuo and the residue was washed with hexane, chromatographed on silica gel,[35] and eluted with hexane. Recrystallization of the chromatographed product from chloroform afforded 271 mg (6%) of **1d** as colorless needles, mp 234–235 °C, indicated to be 98% pure by GLC: ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1, H_1), 7.78 (s, 1, H_4), 7.65 (s, 1, H_7); uv ($CHCl_3$) 256 nm (ϵ 27 000), 266 (41 000), 297 (48 000); mass spectrum *m/e* 344 (24), 342 (71), 340 (100), 338 (64), 277 (22), 275 (19), 203 (26), 173 (17), 138.5 (17), 137.5 (15).

Anal. Calcd for $C_{12}H_3Cl_5O$: C, 42.34; H, 0.89; Cl, 52.08. Found: C, 42.52; H, 1.10; Cl, 52.36.

2,3,6,8-Tetrachlorodibenzofuran (1c). A mixture of 1 equiv of potassium 2,4-dichlorophenolate and 2 equiv of **3** (because it proved more difficult to remove trimeric material than **3** from the reaction product) was heated at 105–110 °C for 6 h, cooled, and extracted with chloroform. The chloroform solution was washed with dilute alkali, dried, and evaporated, and the residue was recrystallized from methanol to give a 34% yield of 2-(2,4-dichlorophenoxy)-4,5-dichloronitrobenzene, 92% pure by GLC. Treatment of 2.0 g (5.7 mmol) of the product with hydrazine and Raney nickel in boiling ethanol afforded 1.77 g (79%) of 2-(2,4-dichlorophenoxy)-4,5-dichloroaniline, indicated to be 97% pure by GLC.

A solution of 10.9 g (0.036 mol) of the aniline and 6.9 g (0.059 mol) of isoamyl nitrite in 700 ml of tetrachloroethylene was heated at 80 °C (bath temperature) for 6 h. Vigorous gas evolution occurred during the first 5 min. The course of the reaction was followed by GLC. The reaction mixture was concentrated in vacuo and the residue was chromatographed on alumina and eluted with hexane–benzene (95:5). Recrystallization of the eluted product from chloroform yielded 382 mg (3.7%) of **1c** as colorless needles: 98.5% pure (GLC); mp 202–203 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1, H_1), 7.78 (s, 1, H_4), 7.77 (d, 1, J = 1.9 Hz, H_9), 7.53 (d, 1, J = 1.9 Hz, H_7); ir ($CHCl_3$) 1656, 1606, 1481, 1430, 1394, 1113, 879 (isolated aromatic CH bend), 866, 854 cm^{-1} (CCl); uv ($CHCl_3$) 250 nm (ϵ 43 000), 260 (52 500), 285 (27 400), 297 (32 000), 314 (14 100); mass spectrum *m/e* 308 (48), 306 (100), 304 (80), 243 (39), 241 (41), 171 (56), 153 (23), 132 (18), 86 (25), 85 (34).

Anal. Calcd for $C_{12}H_4Cl_4O$: C, 47.11; H, 1.32; Cl, 46.34. Found: C, 47.00; H, 1.42; Cl, 46.57.

1c was less conveniently prepared in comparable yield by the aqueous acetic acid–sodium nitrite procedure.

2,4,6-Trichlorodibenzofuran (1b). Heating a mixture of 45.1 g (0.22 mol) of potassium 2,4-dichlorophenolate and 43.0 g (0.22 mol) of 2,3-dichloronitrobenzene at 105–110 °C for 23 h afforded after workup 42.5 g (59%) of 2-(2,4-dichlorophenoxy)-3-chloronitrobenzene at a 98% level of purity (GLC). Treatment of 42 g of this with hydrazine and Raney nickel afforded 27.6 g (73%) of 2-(2,4-dichlorophenoxy)-3-chloroaniline, 96% pure (GLC).

A solution of 27.6 g (0.096 mol) of the aniline and 18.0 g (0.15 mol) of isoamyl nitrite (Eastman) in 950 ml of tetrachloroethylene was heated at 80 °C for 6 h. GLC–mass spectrometric analysis indicated the reaction mixture to contain only 19% of **1b**, 70% trichlorodiphenyl ether, 3% tetrachlorodiphenyl ether, and 7% of the presumed trichloroethenyl–diphenyl ether derivative.

With freshly prepared isoamyl nitrite under somewhat more dilute conditions, 15.0 g (0.052 mol) of the aniline and 9.7 g (0.083 mol) of freshly prepared isoamyl nitrite in 750 ml of tetrachloroethylene, the reaction mixture was found to contain (GLC) 28% of **1b**, 55% trichloro- and 6.5% tetrachlorodiphenyl ether, and 11% of the trichlo-

roethenyl derivative. Thus, the proportion of **1b** was increased, but it remained a minor product; the amount of trichloroethenyl derivative was also increased. GLC after silylation indicated no detectable amounts of phenolic products present.

Removal of solvent under reduced pressure from the first reaction solution left a dark orange oil which was chromatographed on alumina. Elution with hexane yielded a white solid which was chromatographed on silica gel and eluted with hexane to give 1.9 g (7%) of **1b:** 98.5% pure (GLC); mp 116–117 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 1, J = 2 Hz, H_1), 7.50 (d, 1, J = 2 Hz, H_3), 7.79 (m, 1, H_9), 7.36 (m, 2, $H_7 + H_8$); mass spectrum m/e 274 (36), 272 (96), 270 (100), 209 (15), 207 (23), 137 (14), 136 (10), 135 (11).

1,3,4,7,8-Pentachlorodibenzofuran (1e). Heating a mixture of equimolar quantities of potassium 2,3,5-trichlorophenolate (**6**) and **3** at 105–110 °C afforded a 30% yield of material indicated by GLC analysis to contain 88% of **9** and 10% of the isomeric ether **10.** Treatment of the crude product with hydrazine and Raney nickel in boiling 95% ethanol afforded 87% of 2-(2,3,5-trichlorophenoxy)-4,5-dichloroaniline, indicated to be 91% pure by GLC.

A solution of 12.0 g (0.034 mol) of the aniline and 6.6 g (0.056 mol) of isoamyl nitrite in 700 ml of tetrachloroethylene was heated at 80 °C for 6 h. The crude oily reaction product was indicated by GLC–mass spectral analysis to contain 55% of **1e,** 20% pentachlorodiphenyl ether, 5% of the isomeric pentaCDBF (not identical with **1d** or its rearrangement product), and 12% of the trichloroethenyl derivative of the pentachlorodiphenyl ether. Purification of this material proved exceedingly difficult and entailed inordinately large losses of product owing to the more than usual difficulty in separating **1e** from its diphenyl ether relative. The crude product was first chromatographed on alumina and the material eluted with hexane–benzene (95:5) was twice chromatographed on silica gel and eluted with hexane. Repeated recrystallization of the eluant from chloroform and then three times from dioxane afforded 30.4 mg of **1e,** indicated by GLC to be 98.7% pure and to contain 1.3% of the corresponding diphenyl ether: ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1, H_9), 7.73 (s, 1, H_6), 7.46 (s, 1, H_2); ir ($CHCl_3$) 1596, 1435, 1413, 1361, 1100, 883 (isolated aromatic CH bend), 856 cm^{-1} (CCl); uv ($CHCl_3$) 263 nm (ϵ 27 000), 272 (40 000), 297 (48 000), 320 (18 000); mass spectrum m/e 344 (22), 342 (63), 340 (100), 338 (70), 277 (18), 205 (22), 171 (15), 170 (24), 169 (16), 138.5 (15).

Similar results were less conveniently realized by the aqueous acetic acid–sodium nitrite procedure.

2,4,6,8-Tetrachlorodibenzofuran (1h). Chlorine was slowly bubbled through a solution of 16.0 g (0.086 mol) of *o,o'*-biphenol in 350 ml of chloroform for 26 h to give 29 g of a white precipitate indicated by GLC to contain 77% of 4,4',6,6'-tetrachloro-2,2'-biphenol and 19% of trichloro material. Two recrystallizations of the crude product from benzene followed by six recrystallizations from hexane yielded 17.0 g (61%) of 4,4',6,6'-tetrachloro-2,2'-biphenol, mp 176–177 °C, 97% pure (GLC).

A solution of 1.0 g (3.1 mmol) of the tetrachlorobiphenol and 1.2 g (6.3 mmol) of *p*-toluenesulfonyl chloride in 10 ml of anhydrous pyridine was allowed to stand for 19 h at room temperature. The reaction mixture was diluted with water and extracted with benzene. The benzene solution was washed with dilute alkali and water, and then dried and evaporated to yield 2 g (100%) of crude ditosylate (**15**), mp 164–173 °C, colorless needles from hexane, mp 183–184 °C.

Anal. Calcd for $C_{26}H_{18}Cl_4O_6S_2$: Cl, 22.43; S, 10.14. Found: Cl, 22.19; S, 10.01.

To a solution of 2.0 g (3.2 mmol) of crude **15** in 10 ml of DMA was added 0.44 g (7.9 mmol) of powdered potassium hydroxide. The reaction mixture was heated with stirring for 1 h at 100–105 °C (bath temperature) and concentrated in vacuo. The solid residue was extracted with chloroform and the chloroform solution was washed with 10% sodium hydroxide solution and water, dried, and evaporated to dryness. Two recrystallizations of the residual solid from chloroform afforded 283 mg (29%) of **1h** as colorless needles: mp 198–200 °C; 99% pure (GLC); ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2, J = 3 Hz, $H_1 + H_9$), 7.52 (d, 2, J = 3 Hz, $H_3 + H_7$); ir ($CHCl_3$) 1600, 1490, 1439, 1379, 1176, 870 cm^{-1}; uv ($CHCl_3$) 257 nm (ϵ 17 000), 294 (18 600), 310 (5800), 323 (5800); mass spectrum m/e 308 (55), 306 (100), 304 (86), 243 (21), 241 (22), 171 (22), 153 (22), 152 (18), 121.5 (15), 120.5 (14).

Anal. Calcd for $C_{12}H_4Cl_4O$: C, 47.11; H, 1.32. Found: C, 47.04; H, 1.28.

2,3,7,8-Tetrachlorodibenzofuran (1i). This was prepared essentially as described by Kende et al.[19,20] Heating 244 g (0.71 mol) of benzidine-2,2'-disulfonic acid in 1300 g of 50% aqueous sodium hydroxide in a stainless steel bomb at 280 °C for 50 h yielded 17.5 g (9%) of 3,7-diaminodibenzofuran dihydrochloride, free base mp 148–150 °C (lit. mp 152 °C).

To a stirred solution at 0 °C of 17.2 g (0.064 mol) of 3,7-diaminoDBF dihydrochloride in 1 l. of 25% hydrochloric acid was added, dropwise, a solution of 10.1 g (0.15 mol) of sodium nitrite in 100 ml of water. Stirring was continued for 1 h, after which the cold solution was poured in portions into a boiling suspension of freshly prepared cuprous chloride in 450 ml of water (prepared by adding an aqueous solution of 9.8 g of sodium metabisulfite and 5.9 g of sodium hydroxide to a warm aqueous solution of 45.4 g of copper sulfate and 12.3 g of sodium chloride). The reaction mixture was heated at reflux for 2 h, cooled, and extracted with chloroform. The chloroform solution was washed with dilute hydrochloric acid and salt water, dried, and evaporated to give 17.6 g of brown, solid residue which was chromatographed on silica gel and eluted with hexane. Recrystallization of the chromatographed product from hexane gave 7.9 g (53%) of 3,7-diCDBF (**1l**), >98% pure by GLC.

Chlorine was slowly bubbled into a stirred solution at room temperature of 2.0 g (6.5 mmol) of **1l** in 150 ml of chloroform containing a few crystals of ferric chloride and iodine, and the reaction was followed by GLC. Chlorination was halted when significant amounts of the difficultly separable pentachloro homologues began to appear. Concentration of the solution left 2.9 g of brown solid residue indicated by GLC and mass spectral analysis to consist of 68% of **1i,** 24% of triCDBF, 4.5% of two other tetraCDBF isomers, and 3% of three pentaCDBF isomers. Six recrystallizations of this material from isooctane afforded 140 mg (5.4%) of **1i:** 98% pure by GLC; mp 227–228 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 2, $H_1 + H_9$), 7.72 (s, 2, $H_4 + H_6$); uv ($CHCl_3$), 259 nm (ϵ 15 000), 306 (15 000), 316 (14 000); mass spectrum m/e 308 (51), 306 (100), 304 (79), 243 (19), 241 (19), 205 (10), 171 (16), 153 (12), 152 (9), 85 (10).

Anal. Calcd for $C_{12}H_4Cl_4O$: C, 47.11; H, 1.32. Found: C, 47.22; H, 1.37.

2,3,7-TriCDBF (1f). Chlorine was bubbled slowly through a stirred solution of 1.7 g of **1l** in 170 ml of glacial acetic acid at 50 °C (bath temperature) and reaction was followed by GLC. Chlorine introduction was stopped after 2 h and the solution, after being allowed to stand at room temperature overnight, was found to contain (GLC) 23% **1l,** 61% **1f,** 2% of a second triCDBF, 11% of three tetraCDBF isomers, and 3% of four pentaCDBF isomers. Chlorination in chloroform proved no more satisfactory. The solution was diluted with water and the precipitate was recrystallized several times from chloroform and chromatographed on silica gel and then on alumina, eluting with hexane containing gradually increasing amounts of benzene. Attempts to effect further purification of the chromatographed material by recrystallization from a variety of solvents proved unavailing. A useful purification was, however, achieved on an analytical scale by HPLC. A solution of 24 mg of impure material (69% **1f,** 30% **1l,** and 1% tetraCDBF by GLC) in 800 μl of warm dioxane was injected in 100-μl portions onto a Zorbax ODS column, 0.8 × 25 cm, and eluted with methanol–0.01 M aqueous phosphoric acid, 84:16. Near baseline separation of peaks, with a reasonable retention time of 40–50 min for the **1f** peak, was achieved. The middle peak was collected and the product was recrystallized from chloroform to give 6.8 mg of **1f:** 97% pure by GLC; mass spectrum m/e 274 (34), 272 (93), 270 (100), 209 (18), 207 (25), 137 (24), 136 (27), 135 (22), 103.5 (17), 86 (19).

2,3,9-Trichlorodibenzofuran (1g). A solution of 1.0 g (3.5 mmol) of 2-(*m*-chlorophenoxy)-4,5-dichloroaniline (prepared by condensation of potassium *m*-chlorophenolate with **3** followed by hydrazine–Raney nickel reduction of the nitro group) and 0.65 g (5.6 mmol) of isoamyl nitrite in 50 ml of tetrachloroethylene was heated at 80 °C for 6 h. GLC analysis indicated the reaction mixture to contain 29% trichlorodiphenyl ether, 27% **1g,** 14% **1f,** and 8% trichloroethenyl derivative. The solvent was removed in vacuo and the residual orange oil was chromatographed on alumina. The early fractions obtained on elution with hexane contained **1g** and **1f** in a >9:1 ratio. The combined early fractions, 15 mg, composed of (GLC) 71% **1g,** 3% **1f,** and 26% of the reduced diphenyl ether, was chromatographed on silica gel, eluted with hexane, and the eluent (8 mg) was twice recrystallized from chloroform to give 4 mg of **1g,** 95% pure by GLC, containing 3% **1f** and 2% of the diphenyl ether. The structure of **1g** is supported by the ^{1}H NMR spectrum ($CDCl_3$): δ 8.5 (s, 1, H_1), 7.85 (s, 1, H_4), 7.25–7.8 (m, 3, H_6, H_7, H_8); mass spectrum m/e 274 (34), 272 (93), 270 (100), 209 (18), 207 (25), 137 (22), 136 (21), 135 (20), 86 (14).

1,2,7,8-Tetrachlorodibenzofuran (1k). Chlorine was passed through a solution, maintained at 70 °C (bath temperature), of 5.0 g (0.03 mol) of DBF in 150 ml of glacial acetic acid for a period of 50 h to give a reaction mixture indicated by GLC–mass spectral analysis to be composed of 41% **1i,** 21% **1k,** 6.5% of two other tetraCDBF isomers, 25% of triCDBF isomers, and 6% of pentaCDBF isomers. Repeated recrystallization of precipitated material from glacial acetic acid afforded 0.73 g indicated by GLC to consist of 56% **1i** and 43%

1k. The identity of **1i** was confirmed by direct GLC comparison with a sample of the compound prepared by the method of Kende et al. The structural assignment of **1k** was indicated by analysis of the ^{1}H NMR spectrum of the mixture, which also accorded with the presence in the mixture of **1i** and **1k** in a roughly 1:1 ratio. The ^{1}H NMR data are tabulated as follows.

Chemical shift, δ	Proton ratios
8.36	1.9
7.92	4.4
7.67	6.9
7.54	1.6
7.48	1.6
7.33	1.0

The peaks at δ 7.67 and 7.92 are assignable, respectively, to the 4,6 and 1,9 protons of **1i**. The δ 7.33, 7.48, and 7.54 signals taken with a signal buried in the δ 7.67 peak are interpretable as a pair of doublets for the 3,4 protons of **1k**. The signal of the 6 proton of **1k** is also presumably buried in the δ 7.67 peak and the δ 8.36 signal can be assigned to the deshielded 9 proton of this isomer.

A solution of 12 mg of a mixture indicated (GLC) to consist of 5.5% triCDBF, 37% **1k**, 51% **1i**, and 5.5% pentaCDBF in 400 μl of warm dioxane was injected (4 × 100 μl) into the HPLC equipped for recycle with two 0.8 × 25 cm Zorbax ODS columns, at 1100 psi and 55 °C, developing solvent 90% methanol, 10% 0.01 M aqueous phosphoric acid. After one pass through, four nonbaseline separated peaks were observed. The third peak was recycled twice. Collection of the **1k** fraction gave 2 mg indicated by GLC to consist of 96% **1k** and 4% pentaCDBF material: mass spectrum *m/e* 308 (51), 306 (100), 304 (79), 243 (17), 241 (16), 171 (22), 153 (20), 152 (17), 120.5 (16), 85 (18).

Acknowledgments. This work was generously supported by FDA Contract 223-73-2219. We thank Drs. I. H. Pomerantz and A. S. Kende for most helpful discussions and for aid with, respectively, GLC and ^{1}H NMR spectral analyses of the 1,2,7,8- and 2,3,7,8-tetraCDBF mixture, Miss A. D. O'Donnell for the GLC–mass spectral analyses, and Dr. M. Lustig for carrying out some of the early chlorination experiments.

Registry No.—**1a**, 57117-32-5; **1b**, 58802-14-5; **1c**, 57117-37-0; **1d**, 58802-15-6; **1e**, 58802-16-7; **1f**, 58802-17-8; **1g**, 58802-18-9; **1h**, 58802-19-0; **1i**, 51207-31-9; **1k**, 58802-20-3; **2**, 1121-74-0; **3**, 89-69-0; **6**, 58200-72-9; **11**, 58802-21-4; **14**, 58802-22-5; **15**, 58802-23-6; DBF, 132-64-9; 2-(*p*-chlorophenoxy)-4,5-dichloroaniline, 58802-24-7; potassium 2,4,5-trichlorophenolate, 35471-43-3; 2-(2,4,5-trichlorophenoxy)-4,5-dichloroaniline, 58802-25-8; potassium 2,4-dichlorophenolate, 50884-30-5; 2-(2,4-dichlorophenoxy)-4,5-dichloroaniline, 58802-26-9; 2,3-dichloronitrobenzene, 3209-22-1; 2-(2,4-dichlorophenoxy)-3-chloroaniline, 58802-27-0; 2-(2,3,5-trichlorophenoxy)-4,5-dichloroaniline, 58802-28-1; 4,4′,6,6′-tetrachloro-2,2′-biphenol, 14477-61-3; *p*-toluenesulfonyl chloride, 98-59-9; *o,o′*-biphenol, 1806-29-7.

References and Notes

(1) Presented in part at the 9th Annual Conference on Trace Substances in Environmental Health, University of Missouri, Columbia, Mo., June 1975, proceedings in press.
(2) D. Firestone, J. Ress, N. L. Brown, R. P. Barron, and J. N. Damico, *J. Assoc. Off. Anal. Chem.*, **55**, 85 (1972).
(3) J. R. Plimmer, J. M. Ruth, and E. A. Woolson, *J. Agric. Food Chem.*, **21**, 90 (1973).
(4) J. G. Vos, J. H. Koeman, H. L. van der Maas, M. C. ten Noever de Brauw, and R. H. de Vos, *Food Cosmet. Toxicol.*, **8**, 625 (1970).
(5) J. A. G. Roach and I. H. Pomerantz, *Bull. Environ. Contam. Toxicol.*, **12**, 338 (1974).
(6) G. W. Bowes, M. J. Mulvihill, B. R. T. Simoneit, A. L. Burlingame and R. W. Risebrough, *Nature (London)*, **256**, 305 (1975).
(7) G. W. Bowes, M. Mulvihill, M. R. DeCamp, and A. S. Kende, *J. Agric. Food Chem.*, in press.
(8) R. D. Kimbrough, *Arch. Environ. Health*, **25**, 125 (1972).
(9) Panel on Hazardous Trace Substances, *Environ. Res.*, **5**, 249 (1972).
(10) Proceedings of NIEHS Conference on Toxicity of Chlorinated Dibenzo-*p*-dioxins and Dibenzofurans, *Environ. Health Persp., Exp. Issue 5* (1973).
(11) J. S. Taylor, *Cutis*, **13**, 585 (1974).
(12) B. A. Schwetz et al., in "Chlorodioxins-Origin and Fate", E. H. Blair, Ed., *Adv. Chem. Ser.*, **No. 120**, 55–69 (1973).
(13) A. Poland and E. Glover, *Mol. Pharmacol.*, **9**, 736 (1973).
(14) J. S. Taylor, personal communication.
(15) A. P. Gray, S. P. Cepa, and J. S. Cantrell, *Tetrahedron Lett.*, 2873 (1975).
(16) A. P. Gray, S. P. Cepa, I. J. Solomon, and O. Aniline, *J. Org. Chem.*, following paper in this issue.
(17) W. E. Parham in "Heterocyclic Compounds", Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1951, pp 124–136.
(18) G. M. Badger, "The Chemistry of Heterocyclic Compounds", Academic Press, New York, N.Y., 1961, pp 140–141.
(19) A. S. Kende, J. J. Wade, M. DeCamp, D. Ridge, and A. Poland, Abstracts, 167th National Meeting of the American Chemical Society, Los Angeles, Calif., 1974, No. ORGN-130; manuscript in preparation.
(20) (a) A. S. Kende, personal communication. (b) A reviewer has pointed out that other factors such as a steric effect arising from solvation of the nitro group may also be involved.
(21) J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).
(22) H. Gilman, M. W. Van Ess, and D. M. Hayes, *J. Am. Chem. Soc.*, **61**, 643 (1939).
(23) N. M. Cullinane and C. G. Davies, *Recl. Trav. Chim. Pays-Bas*, **55**, 881 (1936).
(24) Kende et al.[19,20] report the preparation of **1a** and **1c** by this route using the aqueous acid procedure.
(25) Kende et al.[19,20] have obtained impure **1f** by an alternative route.
(26) D. C. DeJongh and R. Y. Van Fossen, *J. Org. Chem.*, **37**, 1129 (1972).
(27) S. Yamashiro, *Bull. Chem. Soc. Jpn.*, **17**, 10 (1942).
(28) S. Yamashiro, *J. Chem. Soc. Jpn.*, **59**, 945 (1938).
(29) S. Yamashiro, *Bull. Chem. Soc. Jpn.*, **16**, 6, 61 (1941).
(30) J. Van Dijk, J. J. van Daalen, and G. B. Paerels, *Recl. Trav. Chim. Pays-Bas*, **93**, 72 (1974).
(31) For analysis of ir spectra of related CDBF derivatives, see J.-Y. T. Chen, *J. Assoc. Off. Anal. Chem.*, **56**, 962 (1973).
(32) Activated Raney nickel packed under water from Research Organic/Inorganic Chemical Corp., water replaced by 95% ethanol before use.
(33) R. Q. Brewster and T. Groening, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 446.
(34) Alcoa Grade F-20, 80–200 mesh, heated at 150 °C for at least 4 h before use.
(35) Grace Division Chemical, Grade 62, 60–200 mesh, heated at 150 °C for at least 4 h before use.