or $LiAlH_4$ reductions led to product racemization, in agreement with previous reports.[5]

Best results were consistently obtained by using borane–THF for 1–2 h, depending on the amino acid being reduced. Under the described conditions, the carboxylic acid functions were reduced selectively in the presence of the N-terminal urethane bond. This was evident by the carbonyl IR absorption at 1690 cm^{-1} and the expected 1.4-ppm resonance of the Boc group in the NMR. The properties of some representative amino alcohols prepared by this procedure appear in Table I. All recovered alcohols were shown by TLC to contain a single component, with EtOAc and chloroform–methanol (9:1, 1:1) for plate development. Optical purity was conserved in agreement with studies by Meyers,[5] who demonstrated retention of optical activity when borane–dimethyl sulfide was used to reduce free amino acids to alcohols.

Acknowledgment. This work was supported by a grant from the Muscular Dystrophy Association of America.

Synthesis of Nonachloro-3-phenoxyphenol. Carbon-13 Nuclear Magnetic Resonance Spectra of Polychlorinated Intermediates

Max Deinzer,* Terry Miller, Jack Lamberton, and Brian Arbogast

Environmental Health Sciences Center and Department of Agricultural Chemistry, Oregon State University, Corvallis, Oregon 97331

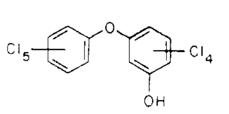
Received February 24, 1981

Analysis of technical pentachlorophenol (PCP) shows the presence of numerous chlorinated byproducts which arise in the manufacturing process.[1] The potential health hazards from exposure to these chemicals is of some concern. It has been shown, for example, that nonachloro-3-phenoxyphenol (I), a contaminant of PCP,[2] has a hemolytic potency at least a hundred times greater than that of PCP,[3] and the need for evaluating other toxicological properties of this compound is apparent. A convenient synthetic procedure is, therefore, needed. We report our methods for synthesizing and purifying I.

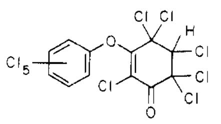
Results and Discussion

Synthesis of I involved perchlorination of *m*-phenoxyphenol with a combination of sulfur monochloride–aluminum chloride–sulfuryl chloride (BMC reagent).[4] The product mixture from the perchlorination reaction was reduced with sodium iodide to obtain I. The overall yield from starting material, *m*-phenoxyphenol, to I was 37%.

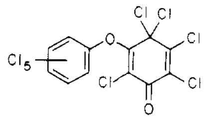
Purification of I was achieved by anion-exchange chromatography followed by extraction of a basic solution of I with 2,2,4-trimethylpentane. Further purification, when necessary, was achieved by chromatography on a reverse-phase RP-18 (25–40 μm) EM-Lichroprep column and then on a silica gel Si-60 column as previously described.[5] The purity of the product was determined by HPLC analysis using a 4.0 × 300 mm Waters Associates μ-Bondapak C-18 column and a 4.6 × 250 mm Lichrosorb Si-60 (5 μ) column.



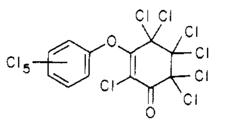
I



II



III



IV

The ^{13}C NMR spectrum of I was obtained in the presence of a spin-relaxation agent, chromium acetylacetonate.[6] The assignment of resonances to the appropriate carbon atoms (Table I) was facilitated by preparing the methyl ether derivative and comparing changes in chemical shifts, $\Delta\delta$, for each carbon atom. A similar comparison was made in Table I for PCP and pentachloroanisole (PCA). The spectrum of I showed two peaks (δ 131.4 and 124.5) that were approximately twice as intense as the rest. These are comparable to those of decachlorodiphenyl ether (δ 131.3 and 123.9). The comparison with diphenyl ether and the observation that carbons β to an oxygen are shifted upfield of benzene (δ 128.5)[7] resulted in the assignments C2′–C6′. Because of the large internuclear distance between these carbon nuclei and the hydroxy group in the adjacent ring, small $\Delta\delta$ values were expected on methylation of the hydroxy group. This was observed (Table I).

The three resonances farthest downfield are clearly associated with oxygen linkages. Comparison with $\Delta\delta$ values for PCP/PCA (Table II) led to the assignment of C1 in I. C1′ and C3 were assigned on the basis of a larger $\Delta\delta$ for the carbon (C3) closer to the site of substitution.

A relatively small $\Delta\delta$ (1.2 ppm) on conversion of the hydroxy to a methoxy group led to the assignment of C5. This value is similar to that observed for the meta carbon atom in PCP/PCA and is consistent with previous reports that meta carbons are not influenced greatly by replacing a hydroxy with a methoxy group.[7] In contrast, ortho and para carbons are shifted significantly by this substitution. The para carbons in PCP and PCA have a $\Delta\delta$ of 5.8 ppm. A similar value ($\Delta\delta$ = 6.2 ppm) for I compared to its methyl ether was used to assign C4. C2 is β to two oxygens, and it was assigned the farthest upfield chemical shift (113.3 ppm). C6, therefore, must appear at 118.3 ppm.

Gas chromatographic-mass spectrometric analysis of the oily residue from perchlorination of *m*-phenoxyphenol indicated the presence of numerous compounds including PCP, hexachloro-2,5-cyclohexadienone, hexachlorobenzene, and chlorinated derivatives with apparent molecular ions (first peak of the isotope clusters) of *m*/*z* 562 (II), 526 (III), and 596 (IV). Mass spectral analysis of the mixture via the probe also showed chlorine clusters with masses above *m*/*z* 680. When II was isolated and reduced by sodium iodide in methanol–hexane solution, I was obtained in 85% yield.

---

[1] B. A. Schwetz, P. A. Keeler, and P. J. Gehring, *Toxicol. Appl. Pharmacol.*, **28**, 151 (1974).

[2] M. Deinzer, J. Lamberton, D. Griffin, and T. Miller, *Biomed. Mass Spectrom.*, 5(10), 566 (1978).

[3] T. L. Miller and M. L. Deinzer, *J. Toxicol. Environ. Health*, **6**, 11 (1980).

[4] M. Ballester, C. Molinet, and J. Castaner, *J. Am. Chem. Soc.*, **82**, 4254 (1960).

[5] M. Deinzer, T. Miller, B. Arbogast, and J. Lamberton, *J. Agric. Food Chem.*, **29**, 679 (1981).

[6] G. C. Levy and J. M. Hewitt, *J. Assoc. Off. Anal. Chem.*, **60**(1), 241 (1977).

[7] G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists" Wiley-Interscience, New York, 1972.

0022-3263/81/1946-4800$01.25/0

Table I. Chemical Shifts for Nonachloro-3-phenoxyphenol and Nonachloro-3-phenoxyanisole

carbon	shift, ppm		$\Delta\delta$, ppm
	phenol[a]	anisole[b]	
1	149.8	152.3	2.5
2	113.3	120.3	7.0
3	146.4	147.1	0.7
4	115.4	121.6	6.2
5	130.1	131.3	1.2
6	118.3	125.3	7.0
1′	147.6	147.5	−0.1
2′	124.5	124.7	0.2
3′	131.4	131.8	0.4
4′	128.3	129.1	0.8
5′	131.4	131.8	0.4
6′	124.5	124.7	0.2
7		60.4	

[a] 100 mg of product in 0.5 mL of CCl_4, 5 mg of chromium acetyl acetonate, and 20 μL of Me_2SO-d_6. [b] 78.7 mg of product in 0.5 mL of CCl_4, 5.5 mg of chromium acetyl acetonate, and 20 μL of Me_2SO-d_6.

Infrared analysis of II revealed absorptions characteristic of an enone; 1725 cm^{-1} for a carbonyl group and 1600 cm^{-1} for a double bond. The proton NMR spectrum indicated the presence of a single proton at 5.3 ppm. Carbon-13 NMR studies on II were carried out in the presence of chromium acetylacetonate (Figure 1a) to help establish the structure. Downfield shifts of 174.5, 154.5, and 145.7 ppm were assigned to a carbonyl carbon atom (C1), the vinyl ether carbon (C3), and the phenyl ether carbon (C1′), respectively. The distinction between C3 and C1′ was made on the basis that the diphenyl ether carbons in I (Table I) and in bis(pentachlorophenyl) ether appear in the vicinity of 146 ppm. Aromatic nuclei appear in the region of 126 ppm for C2′ and C6′, of 131 ppm for C3′ and C5′ and of 131 ppm for C4′. Unlike the ^{13}C NMR spectrum of I, the spectrum of II shows resolved peaks for C2′ and C6′ and for C3′ and C5′ (Figure 1a), suggesting that steric crowding in the molecule results in the presence of distinct rotamers.

In the absence of the nuclear relaxation agent, only three peaks were recorded (Figure 1b). The most intense of these upfield peaks at 70.3 ppm was assigned to the proton-bearing carbon atom, on the basis that it would undergo rapid spin–lattice relaxation and show a significant nuclear Overhauser effect.[7] Off-resonance decoupling confirmed this.

The appearance of two peaks around 83 ppm in this spectrum indicates there are carbon nuclei without protons which also undergo relatively rapid relaxation. This may result from an induced type of relaxation which might be most efficient for nuclei adjacent to the carbon bearing the proton. On this basis the proton-bearing carbon is believed to be C5, and the adjacent carbons C4 and C6 are responsible for the peaks around 83 ppm. The chemical shifts are reasonable for these assignments. The remaining peak at 110.9 ppm in Figure 1a was assigned to C2.

When analysis of II was attempted by HPLC on a silica gel column, hydrogen chloride was eliminated, yielding a yellow compound whose infrared spectrum showed a carbonyl absorption at 1689 cm^{-1} (from 1725 cm^{-1} in II) and two absorptions at 1627 and 1585 cm^{-1} for the double bonds. These spectral data suggest that elimination of chlorine α to the carbonyl occurred, resulting in a 2,5-dienone structure, III. These results also support the structural assignment made for II. Carbon-13 NMR experiments with III were not successful since the compound was unstable under the conditions used. Only a minor amount of III was isolated from the chlorination reaction product mixture.

Table II. Carbon-13 NMR Chemical Shifts for Pentachlorophenol and Pentachloroanisole

carbon	shift, ppm		$\Delta\delta$, ppm
	phenol	anisole	
1	148.1	153.8	5.7
2, 6	119.6	129.5	9.9
3, 5	131.3	133.0	1.7
4	124.8	130.6	5.8
7		61.7	

Compound IV has a molecular ion of m/z 596 and a carbonyl absorption at 1728 cm^{-1} and a double bond absorption at 1598 cm^{-1} in the infrared. This compound, with carbonyl and double bond absorbances almost identical with those of II, showed a very different infrared spectrum in the low-energy region. It was concluded that the difference between II and IV, which were present in a ratio of 14:1 in the product mixture, is simply a chlorine atom in IV in place of the proton in II. The ^{13}C NMR resonances for all carbons are similar to those for II, except C5 which was shifted downfield to 95.81 ppm. Carbons 4 and 6 must have similar magnetic environments since apparently they were not resolved.

In addition to compounds II–IV another component, V, with the molecular ion at m/z 596 was detected in an earlier fraction from the silica chromatography column. This compound had IR absorptions at 1771 (carbonyl) and 1582 cm^{-1} (olefin) and a broad absorption around 1350 cm^{-1}. It did not show a ^{13}C NMR peak around 154 ppm for a vinyl ether carbon as observed for II and IV.

Formation of nonaromatic products from the chlorination of aromatic substrates is well established.[8] Noncatalytic chlorination of diphenyl ether[9] yields 3,4,5,6-tetrachloro-1-cyclohexen-1-yl ether. 4-Chloroanisole yields 1,3,4,5,6-pentachloro-4-methoxycycylohexene,[10] and 3,4-dimethylphenol yields chlorinated enonone and dienone derivatives.[11] Addition of molecular chlorine to the aromatic π system by using the BMC reagent also yields nonaromatic products[12,13] Chlorine addition followed by hydrogen chloride elimination has been proposed as the mechanism for such transformations,[14] and it can account for products observed in this study.

Experimental Section

Gas chromatographic–mass spectrometric analyses were carried out on a Finnigan 4023 instrument. A Pyrex column (0.32 cm × 4.88 m) packed with 3% OV-101 on 80/100-mesh high-performance Chromosorb W (Johns-Manville Co.) was used for separation. Proton and carbon-13 NMR spectra were obtained on a Varian HA-100 spectrometer and a CFT-80 spectrometer, respectively. Infrared measurements were made on a Perkin-Elmer 457 instrument, and high-resolution mass spectrometric data were obtained on a CEC-21-110B instrument. Melting points (uncorrected) were determined on a Fisher-Jones melting point apparatus.

Nonachloro-3-phenoxyphenol (I). A solution of *m*-phen-

---

(8) P. B. D. de la Mare, *Acc. Chem. Res.*, 7(11), 361 (1974).

(9) W. D. Watson, and H. E. Hennis, *J. Org. Chem.*, 44, 1155 (1979).

(10) W. D. Watson and J. P. Heeschen, *Tetrahedron Lett.*, 695 (1974).

(11) P. B. D. de la Mare and B. N. B. Hannan, *J. Chem. Soc., Chem. Commun.*, 1324 (1971).

(12) C. Glidewell and J. C. Walton, *J. Chem. Soc., Chem. Commun.*, 915 (1977).

(13) A. F. Andrews, C. Glidewell, and J. C. Walton, *J. Chem. Res., Miniprint*, 3683 (1978).

(14) P. B. C. de la Mare, B. N. B. Hannan, and N. S. Isaacs, *J. Chem. Soc., Perkin Trans. 2*, 1389 (1976).

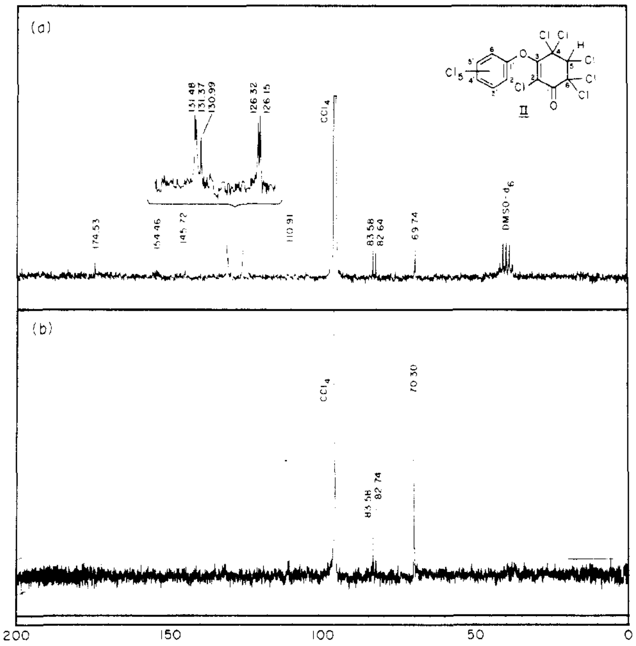


Figure 1. Carbon-13 NMR spectrum of 2,4,4,5,6,6-hexachloro-3-(pentachlorophenoxy)-2-cyclohexenone (II ~60 mg) in (a) carbon tetrachloride (0.5 mL), hexadeuteriodimethyl sulfoxide (20 μL), and chromium acetylacetonate and (b) carbon tetrachloride (1 mL) and hexadeuteriodimethyl sulfoxide (20 ML).

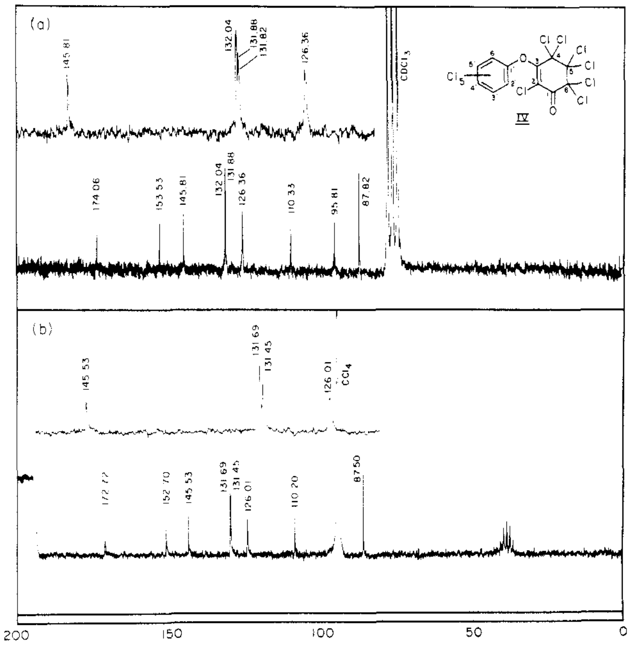


Figure 2. Carbon-13 NMR spectrumof 2,4,4,5,5,6,6-heptachloro-3-(pentachlorophenoxy)-2-cyclohexenone (IV ~70 mg) in (a) carbon tetrachloride (0.5 mL), hexadeuteriodimethyl sulfoxide (20 μL), and chromium acetylacetonate (5.5 mg) and (b) deuteriochloroform (0.5 mL) and chromium acetylacetonate (5.5 mg).

oxyphenol (Eastman Kodak; 2.0 g, 6.7 mmol), sulfuryl chloride (25 mL), and sulfur monochloride (1 mL) was carefully combined with a solution of aluminum chloride (1.0 g) and sulfuryl chloride (25 mL) in a 25 × 300 mm combustion tube (Corning No. 8620) fitted with a 10-mm-bore Rotaflow stopcock (Corning No. 7473-10). The sealed tube was immersed in a water bath at 55 °C for 2 days. The reaction mixture was carefully poured into a beaker containing chloroform (200 mL) and water (150 mL) and stirred. After the mixture cooled, chloroform (100 mL) was added. The phases were separated, and the water layer was extracted with chloroform. The combined chloroform layers were washed with water and with saturated sodium chloride solution. The chloroform layer was dried over anhydrous sodium sulfate and concentrated to dryness.

The residue (5.7 g) was dissolved in hexane (200 mL) and extracted with water, with 2 N sulfuric acid, and again with water. The hexane layer was dried over anhydrous sodium sulfate, filtered, and brought to 250 mL with more hexane. Sodium iodide (4.2 g) in methanol (100 mL) was added to the hexane solution and stirred 20 h. The mixture was concentrated to dryness, redissolved in 1:1 hexane–benzene (200 mL), and extracted with 5% sodium bisulfite solution. The organic layer was washed with water, 2 N sulfuric acid, and water, dried, and concentrated.

Purification of Nonachloro-3-phenoxyphenol (I). Dowex 21K (50–100 mesh) was soaked overnight in 1 N sodium hydroxide. The resin was added to a 2.5 × 33 cm Glenco 3500 column. An additional amount of 1 N sodium hydroxide (200 mL) was pumped through the column. The column was washed with water until the eluant was neutral. The water was washed from the column with methanol.

A 5% solution containing 0.5 g of the reduction product in 1:1 methanol–toluene was pumped onto the column. The column was eluted at 7 mL/min with (a) 1.5 N acetic acid in methanol (500 mL), (b) 1.75 N acetic acid in methanol (500 mL), (c) 2.0 N acetic acid in methanol (1500 mL), and (d) 4.0 N acetic acid in methanol (1000 mL). The eluant was monitored at 280 nm.

The fraction containing I was collected and concentrated to dryness. The residue was dissolved in 0.06 N sodium hydroxide (120 mL) and methanol (75 mL). This solution was extracted with 2,2,4-trimethylpentane. The basic phase was brought to pH 1–2 with dilute sulfuric acid and extracted with methylene chloride. The combined organic layers were concentrated to dryness under nitroten: yield 1.98 g (37.5% based on *m*-phenoxyphenol); exact mass of most abundant ion in molecular ion cluster calcd for $C_{12}HO_2{}^{35}Cl_7{}^{37}Cl_2$ 495.711, found 495.710. Anal. Calcd for $C_{12}HCl_9O_2$: C, 29.05; H, 0.20; Cl, 64.30. Found: C, 29.13; H, 0.27; Cl, 63.67.

Purification of Intermediates. The chloroform solution from the perchlorination reaction was adjusted to 10 mL and transferred onto a chromatography column (37 × 350 mm) containing Silicar^R CC-7 (Mallinckrodt) which had been wet-packed with hexane. Chloroform–hexane (2:8, 800 mL) was pumped through the column. Fractions were collected and monitored on silica TLC plates, and those fractions with spots of the same R_f values were combined and concentrated to dryness. The residue was dissolved in methylene chloride. A white product crystallized when the mixture was allowed to stand. This product was collected and labeled II: mp 183–185 °C; IR (CCl_4) 1725, 1598, 1381, 1360, 1250, 1230, 887, 720 (br) cm^{-1}; mass spectrum, *m/z* 562 ($M^{+}\cdot$); exact mass of most abundant ion in molecular ion cluster calcd for $C_{12}HO_2{}^{35}Cl_9{}^{37}Cl_2$ 565.649, found 565.651. Anal. Calcd for $C_{12}HO_2Cl_{11}$: C, 25.55; H, 0.17; Cl, 68.23. Found: C, 25.42; H, 0.18; Cl, 68.77.

2,2,4-Trimethylpentane containing 5–10% ethyl acetate was added to the mother liquor. Yellow crystals appeared which were collected and labeled III: IR (CCl_4) 1689, 1627, 1585, 1382, 1360, 1275, 1160, 720 (br) cm^{-1}; mass spectrum, *m/z* 526 ($M^{+}\cdot$).

Chloroform–hexane (4:6, 600 mL) was pumped through the column from which II and III had been eluted. A white crystalline product crystallized from the solution after it had been allowed to stand for several days. This material was labeled IV: mp 188–190 °C; IR (KBr pellet) 1728, 1598, 1380, 1363, 1256 (sh) 1240, 1065, 895, 790, 720 cm^{-1} (br); mass spectrum, *m/z* 596 ($M^{+}\cdot$).

Acknowledgment. This investigation was supported by grants from the National Institute of Environmental Health Sciences (Individual Research Grant ES-01968, Program Project Research Grant ES-00040, and Center Grant ES-00210). This paper was issued as Technical Paper No. 5761 from the Oregon Agricultural Experiment Station. We are grateful to Mr. Don Griffin for technical assistance on the mass spectrometer and to Dr. Richard Wielesek, University of Oregon, for high-resolution mass spectrometry data.