Synthesis of Possible Ring-Hydroxylated Metabolites of Diclofop-Methyl

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In the metabolism of diclofop-methyl by tolerant plant species, three ring-hydroxylated metabolites were formed as major metabolites. For conclusive identification of these metabolites, authentic standards were required. Therefore, the following five isomers of hydroxylated diclofop-methyl were synthesized as possible standards for identification of the diclofop-methyl metabolites: methyl 2-[4-(2,4-dichloro-5-hydroxyphenoxy)phenoxy]propanoate, methyl 2-[4-(2,4-dichloro-3-hydroxyphenoxy)phenoxy]propanoate, methyl 2-[4-(2,4-dichloro-6-hydroxyphenoxy)phenoxy]propanoate, methyl 2-[4-(2,5-dichloro-4-hydroxyphenoxy)phenoxy]propanoate, and methyl 2-[4-(2,3-dichloro-4-hydroxyphenoxy)phenoxy]propanoate.

The herbicide diclofop-methyl, methyl 2-[4-(2,4-dichlorophenoxy)phenoxy]propanoate, is rapidly hydrolyzed to the free acid (diclofop) by both resistant and susceptible plant species. Detoxication by tolerant plant species is accomplished by hydroxylation of the dichlorophenoxy moiety of diclofop (Gorbach et al., 1977; Shimabukuro et al., 1979), and glucoside conjugation follows shortly after ring hydroxylation to afford water-soluble metabolites (Shimabukuro et al., 1979). Acid hydrolysis of the glucoside conjugates isolated from wheat gives three isomeric ring-hydroxylated compounds (Gorbach et al., 1977; Tanaka et al., 1986). Although the identities of the hydroxylated metabolites have been investigated, complete identification has not been accomplished.

The hydroxylated metabolites in our study were isolated as methyl esters owing to spontaneous methylation of the free acids in methanol. This unusual property of diclofop and its analogues was first reported by Smith (1976) who discovered that diclofop was readily transformed into diclofop-methyl after being allowed to stand in methanol solution. The preparation of synthetic standards for unequivocal identification of the three hydroxylated metabolites of diclofop-methyl was necessary because initial NMR analysis showed that first-order spectra could not be obtained for all the hydroxylated metabolites (Tanaka et al., 1986). The synthesized intermediates and final products in this study are named according to the substitutive system of nomenclature described by Fletcher et al. (1974) and Rigaudy and Klesney (1979).

EXPERIMENTAL METHODS

Materials. Hydroquinone, 4,6-dichlororesorcinol, 2,4-dichloro-6-nitrophenol, 4-methoxyphenol, hexamethylphosphoramide, and boron tribromide–dimethyl sulfide complex were purchased from Aldrich Chemical Co. The 1-fluoro-4-nitrobenzene, 3,5-dichloro-2-hydroxybenzaldehyde, and 2,5-dichlorohydroquinone were purchased from Eastman Kodak. The 3,5-dichloro-4-hydroxybenzoic acid was obtained from Lancaster Synthesis. Further purification of 4,6-dichlororesorcinol was required before use. Purification was accomplished by dissolving the material in 2-propanol, decolorizing with activated charcoal, concentrating in vacuo, and allowing the material to crystallize from solution. All other chemicals were used as received. The spectral properties of each starting material were taken to verify its identity, and their data are reported below.

Equipment. Electron-impact mass spectra (70 eV) were obtained with use of a solid sample probe on either a Varian CH-5DF or CH-7 spectrometer. The nuclear magnetic resonance (NMR) spectra were taken on a JEOL FX-90Q Fourier transform spectrometer. Tetramethylsilane was used as the internal standard. Thin-layer chromatography (TLC) was performed with 0.25- and 0.50-mm-thick plates of Anasil GF (Analabs). High-performance liquid chromatography (HPLC) was conducted with a Beckman system equipped with two Model 112 high-pressure pumps, a Model 421 solvent program controller, and a Hitachi Model 100-10 variable-wavelength detector. HPLC separations were accomplished on an Altex Ultrasphere ODS-C_{18} column (4.6 mm (i.d.) × 15 cm) of 5-μm particle size. Catalytic reductions were performed with a Parr Series 3910 low-pressure hydrogenation apparatus.

4,6-Dichlororesorcinol (1): MS, m/z (relative intensity) 178 (M^+, 100), 142 (7), 114 (45), 86 (40), 53 (49), 51 (44); ^{1}H NMR (MeOH-d_4) δ 6.55 (s, H, Ar*H*-2), 7.20 (s, H, Ar*H*-5).

2,4-Dichloro-5-(4-nitrophenoxy)phenol (2). Into a 500-mL three-necked flask equipped with reflux condenser, drying tube, thermometer, nitrogen sparging device, and magnetic stirrer was added 200 mL of dry dimethylformamide. The DMF was degassed for 30 min with a stream of N_2, and 8.95 g (50 mmol) of 4,6-dichlororesorcinol was added. The resorcinol was stirred into solution while the solution was being degassed with N_2. Then 5.28 g (110 mmol) of NaH (50% dispersion in mineral oil) was washed free of mineral oil with *n*-hexane and added slowly to the DMF solution. The reaction was stirred for 1 h at room temperature, and then 7.08 g (5.34 mL, 50 mmol) of 1-fluoro-4-nitrobenzene and 5 g of finely powdered anhydrous sodium carbonate were added to the reaction mixture (Tanaka et al., 1979). The reaction was heated at 110–115 °C under a nitrogen atmosphere for 24 h.

The reaction mixture was cooled to room temperature and made acidic with 6 N HCl. The product was extracted with dichloromethane (5 × 100 mL). The extract was washed with water, dried over anhydrous sodium sulfate, and taken to dryness. Highly polar byproducts were removed by passing the product as a benzene solution (benzene may be carcinogenic) through a short column of florisil. The benzene was removed, and the red-orange oil was placed on a column of silica gel (60–200 mesh). Elution was started with a mixture of benzene–hexane (1:1, v/v) to remove the nonpolar byproducts, and pure benzene was subsequently used to elute the dark yellow band that contained the product. The crude product was recrystallized from dichloromethane–hexane solvent: yield 96%; MS, m/z (relative intensity) 299 (M^+, 57), 283 (3), 247 (13), 218 (100); ^{1}H NMR (acetone-d_6) δ 6.92 (s, H, Ar*H*-6), 7.09 (d, 2 H, J = 9.2 Hz, Ar-NO_2), 7.52 (s, H, Ar*H*-3), 8.23 (d, 2 H, J = 9.2 Hz, Ar-NO_2).

2,4-Dichloro-5-methoxy-1-(4-nitrophenoxy)benzene (3). To a diethyl ether solution of **2** was added an ethereal solution of diazomethane (Tanaka et al., 1976). When enough diazomethane (diazomethane may be carcinogenic) was added for the yellow to persist, the reaction was stirred for 1 h. The solvent was removed by rotary evaporation: yield 98%; MS, m/z (relative intensity) 313 (M^+, 100), 299 (7), 261 (26), 232 (84),

217 (66), 189 (45); ^{1}H NMR (MeOH-d_4) δ 3.85 (s, 3 H, OCH_3), 7.04 (s, H, ArH-6), 7.04 (d, 2 H, J = 9.2 Hz, Ar-NO_2), 7.59 (s, H, ArH-3), 8.25 (d, 2 H, J = 9.2 Hz, Ar-NO_2).

4-(2,4-Dichloro-5-methoxyphenoxy)aniline (4). Into a 500-mL reduction flask were added 6.26 g (20 mmol) of **3**, 150 mL of benzene, and approximately 100 mg of PtO_2 (Adams and Cohen, 1961). The reduction was conducted at 45 psi of H_2 pressure for 18 h in a Parr hydrogenation apparatus. After reduction, the catalyst was removed by filtration and the solvent was removed in vacuo: yield 98%; MS, m/z (relative intensity) 283 (M^+, 100), 233 (32), 232 (33), 213 (72), 108 (94); ^{1}H NMR (acetone-d_6) δ 3.74 (s, 3 H, OCH_3), 6.62 (s, H, ArH-6), 6.76 (m, 4 H, Ar-NH_2, AB case), 7.47 (s, H, ArH-3).

4-(2,4-Dichloro-5-methoxyphenoxy)phenol (5). Into a 400-mL beaker were added 5.68 g (20 mmol) of **4** and 10 mL of glacial acetic acid. To the solution of **4** was added 200 mL of 48% fluoboric acid (Cohen et al., 1977), and the resulting suspension was stirred at room temperature for 1 h. The fluoboric acid mixture was cooled to about 5 °C with a salt–ice bath, and a solution of sodium nitrite (1.93 g, 28 mmol) in 20 mL of water was added with vigorous stirring. During nitrite addition, the reaction temperature was maintained at about 5–10 °C. Following addition, the reaction was stirred for 30 min to afford the 4-(2,4-dichloro-5-methoxyphenoxy)phenyldiazonium fluoborate: ^{1}H NMR (MeOH-d_4) δ 3.90 (s, 3 H, OCH_3), 7.21 (s, H, ArH-6), 7.22 (d, 2 H, J = 9.2 Hz, ArN_2^+), 7.68 (s, H, ArH-3), 8.61 (d, 2 H, J = 9.2 Hz, ArN_2^+).

Hydrolysis was accomplished by slow addition of the crude diazonium reaction mixture to 400 mL of 18 N sulfuric acid at 130–140 °C. The reaction was heated and stirred for 10 min after completion of addition. The cooled solution was extracted (5 × 100 mL) with dichloromethane. The extract was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was placed on a short Florisil column and eluted with benzene. The product was isolated as a reddish oil, which was placed on a silica gel column and eluted initially with benzene–hexane (1:1, v/v) to remove the nonpolar impurities. The product was then eluted with benzene, affording a brown oil after concentration: yield 38%; MS, m/z (relative intensity) 284 (M^+, 68), 249 (7), 234 (8), 214 (100), 199 (17); ^{1}H NMR (acetone-d_6) δ 3.75 (s, 3 H, OCH_3), 6.66 (s, H, ArH-6), 6.86 (s, 4 H, ArOH), 7.49 (s, H, ArH-3).

2,4-Dichloro-5-(4-hydroxyphenoxy)phenol (6). Cleavage was accomplished according to the method of Williard and Fryhle (1980). Into a flame-dried 100-mL flask under an atmosphere of nitrogen were added 1.0 g (3.5 mmol) of **5**, 30 mL of dry 1,2-dichloroethane, and 4.4 g (14 mmol) of boron tribromide–dimethyl sulfide complex. The reaction was stirred and refluxed for about 20 h. Hydrolysis was accomplished by addition of 30 mL of water and stirring for 20 min. The reaction was extracted with diethyl ether, and the ether fraction was washed with 1 M sodium bicarbonate. The product was extracted from the ether phase with 1 N sodium hydroxide. The aqueous NaOH solution of **6** was acidified with concentrated HCl, and **6** was extracted with diethyl ether, dried over Na_2SO_4, and concentrated by rotary evaporation. The concentrated oil was dissolved in benzene and placed on a column (2 cm (i.d.) × 24 cm) containing 16 cm of silica gel (60–200 mesh) covered with about 3 cm of Florisil. The product was eluted with benzene, and the yield was 88%: MS, m/z (relative intensity) 270 (M^+, 90), 235 (54), 207 (28), 200 (100), 199 (56), 178 (23), 133 (19), 109 (72); ^{1}H NMR (acetone-d_6) δ 6.47 (s, H, ArH-6), 6.91 (s, 4 H, ArOH), 7.44 (s, H, ArH-3).

Methyl 2-[4-(2,4-Dichloro-5-hydroxyphenoxy)phenoxy]propanoate (7). To a three-necked 100-mL round-bottom flask equipped with condenser, drying tube, addition funnel, nitrogen inlet, and magnetic stirrer was added 20 mL of dry diglyme (Tanaka and Wien, 1976). The solvent was degassed with N_2, and 1.35 g (5.0 mmol) of **6** was added. Then, 0.58 g (12 mmol) of sodium hydride in 50% mineral oil dispersion was washed free of oil with n-hexane, suspended in 10 mL of diglyme, and added with stirring to the reaction flask. The mixture was heated at 80 °C for 15 min, and then 0.84 g (0.56 mL, 5 mmol) of methyl 2-bromopropanoate in 5 mL of diglyme was slowly added. The reaction was heated at 80 °C for 1 h.

The reaction was cooled, and the mixture was made acidic with 25 mL of 10% sulfuric acid. The acidic solution was extracted (3 × 100 mL) with dichloromethane. The extract was dried over anhydrous sodium sulfate, filtered, and taken to dryness in vacuo. Reaction workup caused partial hydrolysis of the ester; thus, the crude product was refluxed in 25 mL of methanolic HCl for 30 min. Then the methanolic HCl was removed in vacuo, the product was placed on a silica gel column (60–200 mesh), and **7** was eluted with toluene–hexane (10:1, v/v). Final purification was accomplished by TLC using benzene–acetone (6:1, v/v) as the developing solvent: product R_f 0.42; yield 61%; MS, m/z (relative intensity) 356 (M^+, 100), 297 (74), 270 (71), 269 (99), 200 (66), 177 (14), 120 (70); ^{1}H NMR (MeOH-d_6) δ 1.56 (d, 3 H, J = 7.0 Hz, CH_3), 3.74 (s, 3 H, COOCH_3), 6.43 (s, H, ArH-6), 6.91 (s, 4 H, OArO), 7.37 (s, H, ArH-3).

3,5-Dichloro-4-hydroxybenzoic acid (8): MS, m/z (relative intensity) 206 (M^+, 100), 189 (92), 172 (5), 161 (9), 155 (8), 133 (9), 125 (8), 97 (8); ^{1}H NMR (acetone-d_6) δ 7.94 (s, 2 H, ArH-2,6).

Methyl 3,5-Dichloro-4-methoxybenzoate (9). Methylation of **8** was accomplished by the same procedure described for methylation of **2**: yield 97%; MS, m/z (relative intensity) 234 (M^+, 72), 203 (100), 169 (8), 160 (7), 140 (6), 132 (4), 111 (8), 97 (14); ^{1}H NMR (acetone-d_6) δ 3.89 (s, 3 H, OCH_3), 3.94 (s, 3 H, COOCH_3), 7.93 (s, 2 H, ArH-2,6).

Methyl 3,5-Dichloro-4-methoxy-2-nitrobenzoate (10). Concentrated nitric acid (100 mL) was cooled in an ice bath, and 100 mL of concentrated sulfuric acid was slowly added to the cold nitric acid. While the reaction temperature was held at less than 10 °C, 4.68 g (20 mmol) of **9** was added with stirring (Huntress and Shriner, 1959). The reaction was stirred for 16 h at room temperature and subsequently heated at 60 °C for 1 h. The cooled reaction was slowly poured into ice–water with vigorous stirring. The precipitated product was isolated by filtration, and the moist cake was transferred into 200 mL of ice–water and stirred vigorously. The product was filtered, washed with cold water, and dried: yield 76%; MS, m/z (relative intensity) 279 (M^+, 100), 248 (69), 233 (12), 218 (28), 175 (29), 174 (42), 161 (21), 131 (34), 96 (25); ^{1}H NMR (acetone-d_6) δ 3.90 (s, 3 H, OCH_3), 4.06 (s, 3 H, COOCH_3), 8.12 (s, H, ArH-6).

Methyl 3,5-Dichloro-4-methoxy-2-(4-methoxyphenoxy)benzoate (11). To a 250-mL three-necked round-bottom flask fitted with drying tube and stirrer were added 3.10 g (25 mmol) of 4-methoxyphenol and 10 mL of dry diethyl ether. A 50% oil dispersion of NaH (1.44 g, 30 mmol) was washed with n-hexane and added to the reaction vessel. After gas evolution ceased, the ether was removed with a stream of nitrogen and 2.79 g (10 mmol) of **10** in 40 mL of hexamethyl phosphoramide (HMPA) was added (Kornblum et al., 1976). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 18 h. The reaction was made acidic with 100 mL of 10% sulfuric acid, extracted with diethyl ether, washed with water, and taken to dryness in vacuo.

The crude solid product was dissolved in diethyl ether and treated with ethereal diazomethane to ensure complete esterification of the carboxyl group. The product was purified on a silica gel column (60–200 mesh) with a benzene–n-hexane (1:1, v/v) mixture for elution: yield 73%; MS, m/z (relative intensity) 356 (M^+, 69), 325 (8), 310 (4), 262 (5), 138 (32), 123 (100), 57 (35); ^{1}H NMR (acetone-d_6) δ 3.68 (s, 3 H, COOCH_3), 3.75 (s, 3 H, ArOCH_3), 3.98 (s, 3 H, ArCl_2OCH_3), 6.75 (d, 2 H, J = 8.8 Hz, ArOCH_3), 6.87 (d, 2 H, J = 8.8 Hz, ArOCH_3), 7.91 (s, H, ArH-6).

3,5-Dichloro-4-methoxy-2-(4-methoxyphenoxy)benzoic Acid (12). Into a round-bottom flask were placed 3.56 g (10 mmol) of **11** and 100 mL of Claisen's alkali (Tarbell et al., 1960). The reaction was refluxed for 1 h, diluted with 200 mL of water, and extracted with diethyl ether to remove nonpolar byproducts. The ether layer was discarded. The aqueous layer was made acidic with 6 N HCl, and upon cooling, the product precipitated from solution. The product was isolated by filtration, washed with cold water several times, and recrystallized from 2-propanol–water mixture: yield 90%; MS, m/z (relative intensity) 342 (M^+, 45), 306 (4), 219 (98), 204 (7), 124 (100); ^{1}H NMR (acetone-d_6) δ 3.66 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3),

6.74 (d, 2 H, J = 9.0 Hz, $ArOCH_3$), 6.88 (d, 2 H, J = 9.0 Hz, $ArOCH_3$), 7.91 (s, H, Ar*H*-6).

2,6-Dichloro-3-(4-methoxyphenoxy)phenyl Acetate (13). Into a round-bottom flask were added 4 g (11.7 mmol) of **12**, 20 mL of quinoline, 10 mL of acetic acid, 10 mL of acetic anhydride, and 0.5 g of activated copper that was prepared according to the method of Brewster and Groening (1959). The reaction flask was degassed with nitrogen and heated at 190 °C for about 8 h under an N_2 atmosphere. After reaction, 100 mL of cold water was added and the reaction was made acidic with concentrated HCl. The product was extracted with diethyl ether, and the extract was passed through a column of silica gel and Florisil (cf. synthesis of **6**). The ether eluate was made basic with 2 N NaOH, and the product was extracted again with ether. The ether extract was again passed through a silica gel plus Florisil column and taken to dryness in vacuo: product yield 58%; MS, m/z (relative intensity) 326 (M^+, 26), 284 (100), 269 (13), 214 (12), 178 (40), 177 (5), 43 (46); ^1H NMR (MeOH-d_4) δ 2.15 (s, 3 H, $COCH_3$), 3.77 (s, 3 H, OCH_3), 6.33 (d, H, J = 9.2 Hz, Ar*H*-6), 6.91 ((s, 4H, $ArOCH_3$), 7.15 (d, H, J = 9.2 Hz, Ar*H*-5).

2,6-Dichloro-3-(4-methoxyphenoxy)phenol (14). Into a reaction flask were added 2.2 g (6.7 mmol) of **13** and 100 mL of Claisen's alkali (Tarbell et al., 1960). The mixture was heated at reflux for 2 h, and after cooling, the reaction was made acidic with concentrated HCl. The product was extracted with diethyl ether, and the ether extract was passed through a silica gel and Florisil column (cf. synthesis of **6**): yield 99%; MS, m/z (relative intensity) 284 (M^+, 100), 269 (22), 233 (6), 214 (24), 213 (14), 178 (40), 177 (24), 123 (20); ^1H NMR (acetone-d_6) δ 3.78 (s, 3 H, OCH_3), 6.41 (d, H, J = 9.2 Hz, Ar*H*-4), 6.97 (s, 4 H, $ArOCH_3$), 7.23 (d, H, J = 9.2 Hz, Ar*H*-5).

2,6-Dichloro-3-(4-hydroxyphenoxy)phenol (15). Cleavage of the methyl ether was accomplished as described for synthesis of **6**. In this reaction, 1.91 g (6.7 mmol) of **14** was treated with 6.3 g (20.1 mmol) of boron tribromide–dimethyl sulfide complex: yield 94%; MS, m/z (relative intensity) 270 (M^+, 55), 235 (8), 200 (76), 57 (100); ^1H NMR (acetone-d_6) δ 6.39 (d, H, J = 9.2 Hz, Ar*H*-4), 6.89 (s, 4 H, ArOH), 7.25 (d, H, J = 9.2 Hz, Ar*H*-5).

Methyl 2-[4-(2,4-Dichloro-3-hydroxyphenoxy)phenoxy]-propanoate (16). Reaction was performed as described for synthesis of **7** using 1.76 g (6.5 mmol) of **15** in the coupling reaction. Product purification was by TLC using a solvent of benzene–acetone (6:1, v/v): R_f 0.54; yield 76%; MS, m/z (relative intensity) 356 (M^+, 100), 297 (80), 270 (75), 269 (87), 200 (44), 177 (20), 120 (35); ^1H NMR (MeOH-d_4) δ 1.58 (d, 3 H, J = 7.0 Hz, CH_3), 3.74 (s, 3 H, $COOCH_3$), 6.37 (d, H, J = 9.2 Hz, Ar*H*-6), 6.89 (s, 4 H, OArO), 7.17 (d, H, J = 9.2 Hz, Ar*H*-5).

3,5-Dichloro-2-hydroxybenzaldehyde (17): MS, m/z (relative intensity) 190 (M^+, 100), 189 (80), 172 (17), 144 (18), 133 (26), 126 (13), 97 (22), 63 (46); ^1H NMR (acetone-d_6) δ 7.78 (d, H, J = 2.6 Hz, Ar*H*-4), 7.86 (d, H, J = 2.6 Hz, Ar*H*-6), 10.06 (s, H, C*H*O).

3,5-Dichlorocatechol (18). Oxidation of the aldehyde group of **17** was accomplished by the method of Dakin (1961). To 9.5 g (50 mmol) of **17** was added 50 mL of 2 N NaOH, and the aldehyde was allowed to stir into solution. Then 7.1 mL of 30% H_2O_2 was added and the reaction mixture was stirred with heating at 45 °C overnight. The reaction was neutralized with glacial acetic acid, and the product upon being allowed to stand precipitated from solution. The isolated product was purified by dissolving in water under basic conditions and reprecipitating the product under acidic conditions: yield 77%; MS, m/z (relative intensity) 178 (M^+, 100), 142 (28), 114 (83), 79 (53), 57 (50); ^1H NMR (acetone-d_6) δ 6.83 (d, H, J = 2.6 Hz, Ar*H*-6), 6.88 (d, H, J = 2.6 Hz, Ar*H*-4).

3,5-Dichloro-2-(4-nitrophenoxy)phenol (19a). Procedures for synthesis and initial purification of **19a** were the same as employed for **2**. After product purification, the two isomers (cf. Scheme III) were separated by TLC. Preparative TLC plates were developed in a solvent of benzene–acetone (9:1, v/v), with **19a** having R_f 0.29 and **19b** having R_f 0.42. Reaction yield for **19a** was 21%, and yield for **19b** was 38%: MS, m/z (relative intensity) 299 (M^+, 100), 282 (28), 269 (5), 252 (27), 218 (26), 177 (15); ^1H NMR (acetone-d_6) δ 7.10 (d, 2 H, J = 9.2 Hz, ArNO_2), 7.10 (d, H, J = 2.6 Hz, Ar*H*-6), 7.15 (d, H, J = 2.6 Hz, Ar*H*-4), 8.26 (d, 2 H, J = 9.2 Hz, ArNO_2).

2,4-Dichloro-6-methoxy-1-(4-nitrophenoxy)benzene (20). Reaction of **19a** with diazomethane was the same as that used for preparation of **3**: yield 93%; MS, m/z (relative intensity) 313 (M^+, 100), 283 (13), 252 (14), 232 (8); ^1H NMR (acetone-d_6) δ 3.87 (s, 3 H, OCH_3), 7.09 (d, 2 H, J = 9.2 Hz, ArNO_2), 7.27 (s, 2 H, Ar*H*-3,5), 8.25 (d, 2 H, J = 9.2 Hz, ArNO_2).

4-(2,4-Dichloro-6-methoxyphenoxy)aniline (21). Catalytic reduction of **20** was the same as that employed for synthesis of **4**: yield 100%; MS, m/z (relative intensity) 283 (M^+, 100), 249 (7), 233 (10), 213 (6), 108 (56), 65 (41); ^1H NMR (acetone-d_6) δ 3.84 (s, 3 H, OCH_3), 6.77 and 6.79 (inner large peaks of AB case, 4 H, $ArNH_2$), 7.15 (s, H, Ar*H*-5), 7.20 (s, H, Ar*H*-3).

4-(2,4-Dichloro-6-methoxyphenoxy)phenol (22). Formation of the diazonium fluoborate salt of **21** and subsequent hydrolysis to the phenol were accomplished by the same procedure used for the preparation of **5**: yield 44%; MS, m/z (relative intensity) 284 (M^+, 100), 250 (5), 234 (11), 214 (26), 107 (29); ^1H NMR (acetone-d_6) δ 3.83 (s, 3 H, OCH_3), 6.70 and 6.72 (inner large peaks of AB case, 4 H, ArOH), 7.17 (s, 2 H, Ar*H*-3,5).

3,5-Dichloro-2-(4-hydroxyphenoxy)phenol (23). Cleavage of the methyl ether was according to the procedure used for preparation of **6**. In this reaction, 0.93 g (3.26 mmol) of **22** was treated with 4.06 g (13 mmol) of boron tribromide–dimethyl sulfide complex: yield 80%; MS, m/z (relative intensity) 270 (M^+, 100), 200 (4), 177 (3), 109 (5), 94 (80); ^1H NMR (acetone-d_6) δ 6.71 and 6.73 (inner large peaks of AB case, 4H, ArOH), 7.02 (d, H, J = 2.2 Hz, Ar*H*-6), 7.06 (d, H, J = 2.2 Hz, Ar*H*-4).

Methyl 2-[4-(2,4-Dichloro-6-hydroxyphenoxy)phenoxy]-propanoate (24). Reaction was performed as described for the preparation of **7** with 0.13 g (0.49 mmol) of **23**. Purification was by TLC using a solvent of benzene–acetone (6:1, v/v): product R_f 0.50; yield 54%; MS, m/z (relative intensity) 356 (M^+, 100), 297 (79), 270 (71), 269 (88), 177 (18), 120 (53), 94 (63); ^1H NMR (MeOH-d_4) δ 1.53 (d, 3 H, J = 6.6 Hz, CH_3), 3.72 (s, 3 H, $COOCH_3$), 6.76 and 6.78 (inner large peaks of AB case, 4 H, OArO), 6.90 (d, H, J = 2.6 Hz, Ar*H*-5), 6.98 (d, H, J = 2.6 Hz, Ar*H*-3).

2,5-Dichlorohydroquinone (25): MS, m/z (relative intensity) 178 (M^+, 100), 142 (7), 114 (43), 86 (37), 53 (45), 51 (39); ^1H NMR (acetone-d_6) δ 7.05 (s, 2 H, Ar*H*), 8.54 (br s, 2 H, OH).

2,5-Dichloro-4-(4-nitrophenoxy)phenol (26). Synthesis was by the same procedure used for the synthesis of **2**: yield 69%; MS, m/z (relative intensity) 299 (M^+, 100), 269 (6), 225 (25), 218 (44), 177 (15); ^1H NMR (acetone-d_6) δ 7.12 (d, 2 H, J = 9.2 Hz, ArNO_2), 7.24 (s, H, Ar*H*-3), 7.44 (s, H, Ar*H*-6), 8.27 (d, 2 H, J = 9.2 Hz, ArNO_2).

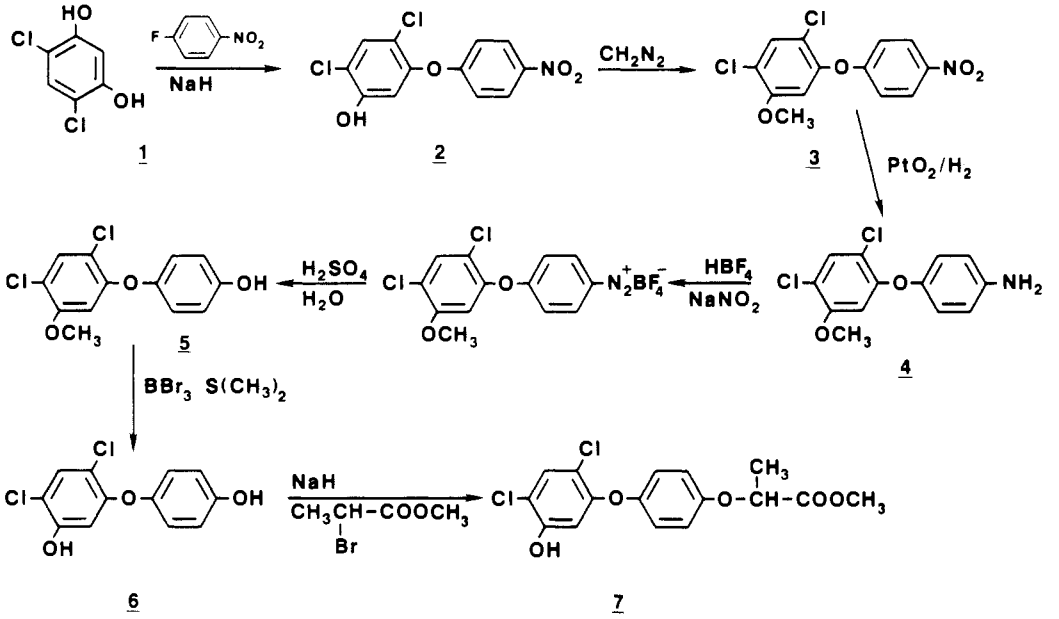
2,5-Dichloro-4-methoxy-1-(4-nitrophenoxy)benzene (27). Synthesis was by the same procedure used for the synthesis of **3**: yield 89%; MS, m/z (relative intensity) 313 (M^+, 100), 298 (37), 246 (6), 232 (12), 196 (9), 189 (19), 161 (8), 141 (18), 76 (47); ^1H NMR (acetone-d_6) δ 3.99 (s, 3 H, OCH_3), 7.09 (d, 2 H, J = 9.2 Hz, ArNO_2), 7.37 (s, H, Ar*H*-6), 7.47 (s, H, Ar*H*-3), 8.25 (d, 2 H, J = 9.2 Hz, ArNO_2).

4-(2,5-Dichloro-4-methoxyphenoxy)aniline (28). Synthesis was by the same procedure used for the synthesis of **4**: yield 99%; MS, m/z (relative intensity) 283 (M^+, 100), 268 (8), 240 (6), 213 (9), 108 (26), 92 (14), 65 (12); ^1H NMR (acetone-d_6) δ 3.90 (s, 3 H, OCH_3), 6.72 (m, 4 H, AB case, $ArNH_2$), 6.91 (s, H, Ar*H*-6), 7.21 (s, H, Ar*H*-3).

4-(2,5-Dichloro-4-methoxyphenoxy)phenol (29). Synthesis was by the same procedure used for the synthesis of **5**: yield 28%; MS, m/z (relative intensity) 284 (M^+, 100), 269 (11), 241 (19), 214 (16), 191 (6), 177 (6), 65 (46); ^1H NMR (acetone-d_6) δ 3.93 (s, 3 H, OCH_3), 6.86 (s, 4 H, ArOH), 7.00 (s, H, Ar*H*-6), 7.23 (s, H, Ar*H*-3).

2,5-Dichloro-4-(4-hydroxyphenoxy)phenol (30). Synthesis was by the same procedure used for the synthesis of **6**. Ether cleavage was performed with 1.13 g (3.96 mmol) of **29** and 4.94 g (15.8 mmol) of boron tribromide–dimethyl sulfide complex: yield 50%; MS, m/z (relative intensity) 270 (M^+, 98), 235 (13), 207 (9), 200 (100), 177 (14), 109 (20), 57 (69); ^1H NMR (acetone-d_6) δ 6.85 (s, 4 H, ArOH), 6.99 (s, H, Ar*H*-3), 7.16 (s, H, Ar*H*-6).

Scheme I



Methyl 2-[4-(2,5-Dichloro-4-hydroxyphenoxy)phenoxy]-propanoate (31). Synthesis was performed as described for the preparation of **7** with 0.53 g (2.0 mmol) of **30**. Purification of the product was by TLC using a solvent of benzene–acetone (6:1, v/v): product R_f 0.46; yield 18%; MS, *m/z* (relative intensity) 356 (M^+, 100), 297 (70), 270 (76), 269 (90), 233 (18), 200 (38), 177 (26), 120 (55); ^{1}H NMR (MeOH-d_4) δ 1.53 (d, 3 H, J = 6.6 Hz, CH_3), 3.71 (s, 3 H, $COOCH_3$), 4.78 (q, H, J = 6.6 Hz, =C*H*), 6.82 (s, 4 H, OArO), 6.94 (s, H, Ar*H*-6), 7.01 (s, H, Ar*H*-3).

Hydroquinone (32): MS, *m/z* (relative intensity) 110 (M^+, 100), 97 (7), 82 (25), 81 (38), 56 (19), 54 (17); ^{1}H NMR (acetone-d_6) δ 6.65 (s, 4 H, Ar), 7.90 (br s, 2 H, OH).

2,3-Dichlorohydroquinone (33). By the method of Conant and Fieser (1923), 40 g (0.36 mol) of **32** was chlorinated in 200 mL of glacial acetic acid at 40–50 °C: yield 34%; MS, *m/z* (relative intensity) 178 (M^+, 100), 142 (94), 114 (87), 86 (53), 79 (99), 73 (89); ^{1}H NMR (acetone-d_6) δ 6.86 (s, 2 H, Ar*H*-5,6), 8.52 (s, 2 H, OH).

2,3-Dichloro-4-(4-nitrophenoxy)phenol (34). Synthesis was by the same procedure used for the synthesis of **2**: yield 66%; MS, *m/z* (relative intensity) 299 (M^+, 100), 218 (81), 177 (20), 125 (24), 111 (36), 97 (43), 71 (53), 58 (72); ^{1}H NMR (acetone-d_6) δ 7.10 (d, 2 H, J = 9.2 Hz, $ArNO_2$), 7.17 (s, H, Ar*H*-5), 7.20 (s, H, Ar*H*-6), 8.17 (d, 2 H, J = 9.2 Hz, $ArNO_2$).

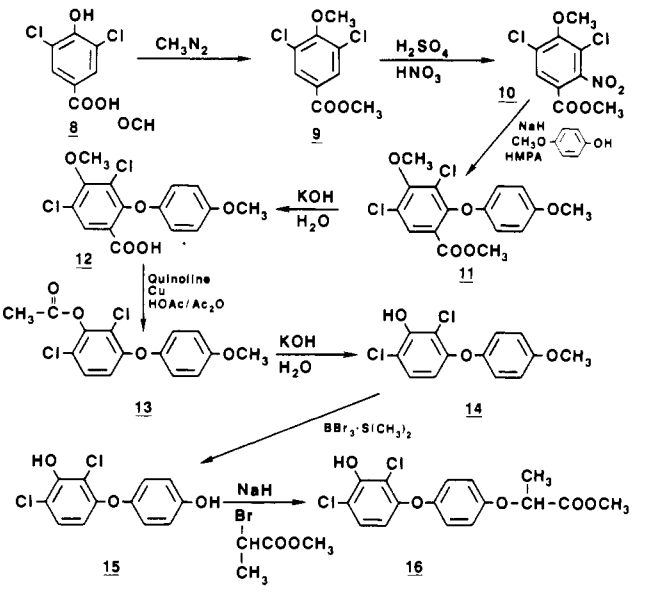
2,3-Dichloro-4-methoxy-1-(4-nitrophenoxy)benzene (35). Synthesis was by the same procedure used for the synthesis of **3**: yield 86%; MS, *m/z* (relative intensity) 313 (M^+, 100), 298 (19), 232 (6), 196 (5), 189 (9), 141 (9), 113 (9); ^{1}H NMR (acetone-d_6) δ 4.00 (s, 3 H, OCH_3), 7.10 (d, 2 H, J = 9.2 Hz, $ArNO_2$), 7.29 (s, H, Ar*H*-6), 7.33 (s, H, Ar*H*-5), 8.27 (d, 2 H, J = 9.2 Hz, $ArNO_2$).

4-(2,3-Dichloro-4-methoxyphenoxy)aniline (36). Synthesis was by the same procedure used for the synthesis of **4**: yield 98%; MS, *m/z* (relative intensity) 283 (M^+, 72), 268 (4), 240 (6), 213 (13), 108 (81), 92 (68), 65 (100); ^{1}H NMR (acetone-d_6) δ 3.90 (s, 3 H, OCH_3), 6.70 (s, 4 H, $ArNH_2$), 6.85 (d, H, J = 9.2 Hz, Ar*H*-6), 7.06 (d, H, J = 9.2 Hz, Ar*H*-5).

4-(2,3-Dichloro-4-methoxyphenoxy)phenol (37). Synthesis was by the same procedure used for the synthesis of **5**: yield 44%; MS, *m/z* (relative intensity) 284 (M^+, 61), 241 (12), 192 (21), 177 (33), 58 (100); ^{1}H NMR (acetone-d_6) δ 3.91 (s, 3 H, OCH_3), 6.83 (s, 4 H, OArO), 6.92 (d, H, J = 9.2 Hz, Ar*H*-6), 7.09 (d, H, J = 9.2 Hz, Ar*H*-5).

2,3-Dichloro-4-hydroxyphenoxy)phenol (38). For ether cleavage, 2.18 g (7.6 mmol) of **37** was treated with 7.1 g (22.8 mmol) of boron tribromide–dimethyl sulfide complex (cf. synthesis of **6**): yield 76%; MS, *m/z* (relative intensity) 270 (M^+, 89), 235 (17), 200 (100), 177 (11), 109 (13), 65 (19); ^{1}H NMR (acetone-d_6) δ 6.82 (s, 4 H, OArO), 6.84 (d, H, J = 9.2 Hz, Ar*H*-6), 7.00 (d, H, J = 9.2 Hz, Ar*H*-5).

Scheme II



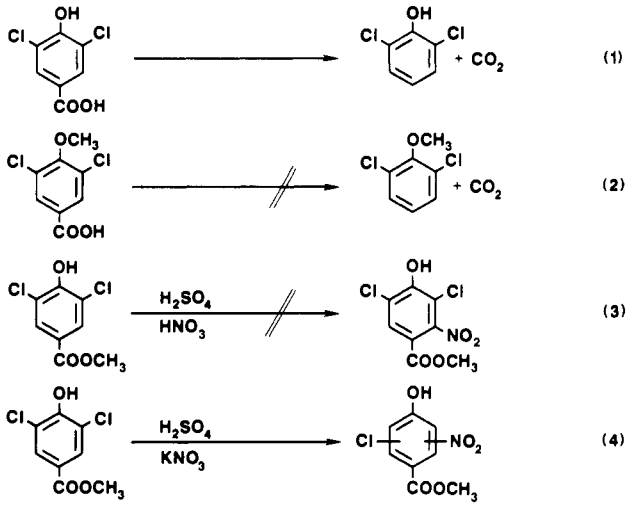
Methyl 2-[4-(2,3-Dichloro-4-hydroxyphenoxy)phenoxy]-propanoate (39). Reaction was performed as described for the synthesis of **7** with 1.57 g (5.8 mmol) of **38**. The product was purified by TLC using a solvent of benzene–acetone (6:1, v/v): product R_f 0.46; yield 21%; MS, *m/z* (relative intensity) 356 (M^+, 100), 297 (77), 270 (77), 269 (92), 200 (34), 177 (20), 120 (36); ^{1}H NMR (MeOH-d_4) δ 1.55 (d, 3 H, J = 7.0 Hz, CH_3), 3.74 (s, 3 H, $COOCH_3$), 6.83 (s, 2 H, Ar*H*-5,6), 6.82 and 6.85 (4 H, inner large peaks of AB case, OArO).

RESULTS AND DISCUSSION

In the initial development of Scheme I, the diazonium fluoborate salt was isolated from the reaction mixture prior to acid hydrolysis; thus, an NMR spectrum was obtained for this salt. However, subsequent studies showed that acid hydrolysis could be performed just as efficiently without product isolation. Therefore, the fluo-

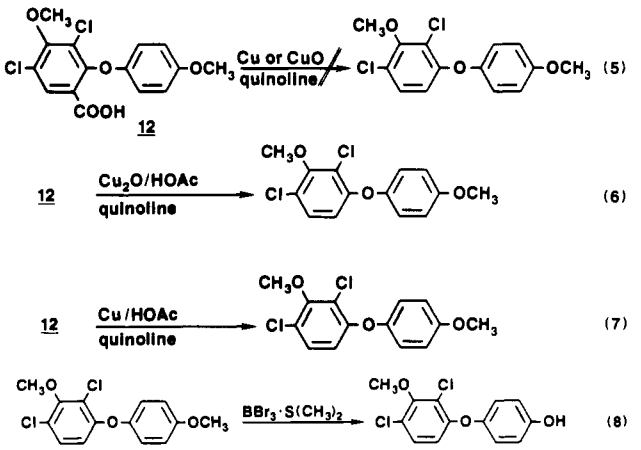
borate intermediates were not isolated in the reaction schemes developed for this study. When **7** (2,4-dichloro-5-hydroxy isomer) was first synthesized, the methyl group protecting the 5-OH moiety was removed after attachment of the methyl 2-propanoate side chain. However, when the methyl ether was cleaved with boron tribromide–dimethyl sulfide complex, the methyl 2-propanoate side chain was also cleaved. Therefore, a low yield of **7** and large quantities of byproducts were obtained by this scheme. To avoid side chain cleavage, the methyl ether was cleaved prior to attachment of the methyl 2-propanoate side chain as shown in Scheme I.

The synthesis of **16** (2,4-dichloro-3-hydroxy isomer) in Scheme II was based on the facile decarboxylation of **8** to yield 2,6-dichlorophenol by refluxing in dimethylaniline (eq 1; Tarbell et al., 1960). However, **12** could not



be decarboxylated in refluxing dimethylaniline. Furthermore, if the hydroxyl group of **8** was methylated, decarboxylation would not take place (eq 2). Therefore, a methoxyl group para to the carboxyl group provided a strong negative effect on the decarboxylation reaction. Attempts were made to alter Scheme II by introducing the nitro group onto the methyl ester of **8**; however, nitration would not take place if the hydroxyl group was not methylated (eq 3). Nitration under nonaqueous conditions with concentrated H_2SO_4 and KNO_3 at less than −15 °C (CCl_4–dry ice bath) gave a nitrated product with concomitant elimination of one chlorine atom (eq 4). Thus, a methylated hydroxyl group was necessary for facile introduction of a nitro group onto the aromatic ring without chlorine elimination. The above findings made it essential that a method be developed for decarboxylation of **12** in Scheme II.

Decarboxylation reactions have been performed with powdered copper or with cuprous oxide in quinoline at reflux temperature (Cohen and Schambach, 1970). Our attempts to decarboxylate **12** with either copper powder or cuprous oxide in refluxing quinoline failed (eq 5). By addition of acetic acid to the cuprous oxide and quinoline, **12** was decarboxylated to give a product in less than 5% yield (eq 6). If activated copper was employed with quinoline and acetic acid, a moderate yield of decarboxylated product was obtained (eq 7). However, the simultaneous cleavage of both methyl ether groups in the subsequent reactions did not take place; only the methyl moiety of the unhindered methoxyl group was cleaved (eq 8). The addition of acetic anhydride to the reaction mixture caused the decarboxylation of **12** to occur in good yield, but surprisingly during the same reaction, the methyl



ether at the 3-position was cleaved and acylated to afford **13** (Scheme II). Thus, the problem of cleaving the hindered 3-OMe group was eliminated.

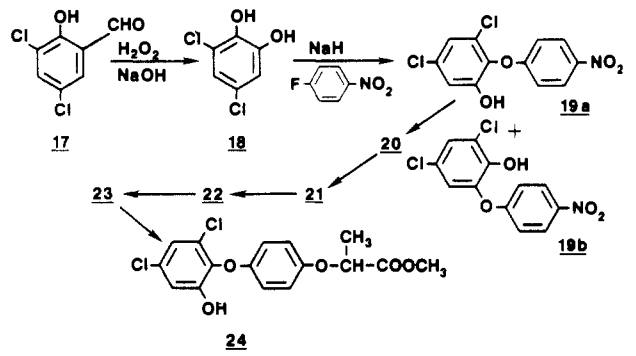
In our first attempts to prepare **24** (2,4-dichloro-6-hydroxy isomer), 2,4-dichloro-6-nitrophenol was used as starting material. Through a series of reactions the diphenyl ether, 3,5-dichloro-2-(4-nitrophenoxy)aniline, was prepared. The amino moiety of this diphenyl ether was to be diazotized and subsequently hydrolyzed to afford a hydroxyl group on the chlorinated ring. The diazotization of the amino moiety was attempted with use of sodium nitrite and sulfuric acid (Hodgson et al., 1960), nitrosylsulfuric acid and orthophosphoric acid (Schoutissen, 1933), and sodium nitrite and fluoboric acid (Cohen et al., 1977). However, all attempts for diazotization with subsequent hydrolysis of the amino moiety failed. Therefore, to prepare the 6-OH isomer, the reaction sequence given in Scheme III was developed from 2,4-dichloro-6-hydroxybenzaldehyde (**17**) as starting material.

After preparation of 3,5-dichlorocatechol (**18**) in Scheme III, attempts were made to monomethylate **18**, which would then afford only one isomer in the subsequent fluoronitrobenzene coupling reaction. The rationale for monomethylation was based on the assumption that the 1-OH group would be preferentially methylated over the 2-OH group because of steric factors. Several different methods (Vyas and Shah, 1967; Newman and Cella, 1974; Jacobson et al., 1987) were tried; however, no method afforded the desired isomer in preferential yield. Therefore, monomethylation was abandoned, and consequently two isomers were obtained in the synthesis of **19a**.

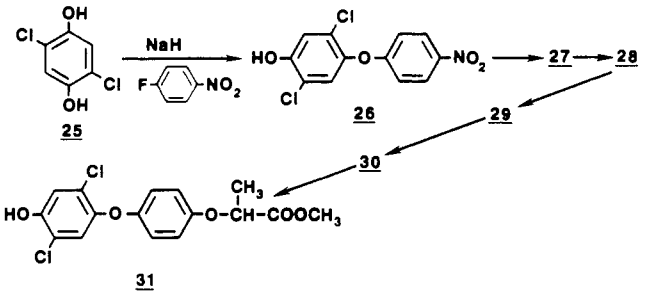
Using **19a** and its structural isomer (**19b**) in the subsequent 5-step reaction sequence given in Scheme III, four isomeric products including **24** were obtained, with each having a molecular mass of m/z 356. The identity of **24** was determined from the other three isomers by the following evidence: (1) From the coupling reaction, **19a** was the least abundant isomer due to steric factors. (2) By TLC, **19a** was more polar than **19b** because its hydroxyl group was less hindered. (3) Methyl ether cleavage of **20** was complete, whereas methyl ether cleavage of the isomer of **20** was incomplete due to steric hinderance. (4) The NMR spectra showed that when the proton on the chlorinated ring was ortho to the hydroxy group, this proton was shifted downfield from the singlet representing the four protons of the nonchlorinated ring. On the other hand, when the proton on the chlorinated ring was ortho to the phenoxy group, this proton was shifted upfield from the four-proton singlet of the nonchlorinated ring.

Scheme IV was employed for the synthesis of **31** (2,5-dichloro-4-hydroxy isomer). The experimental proce-

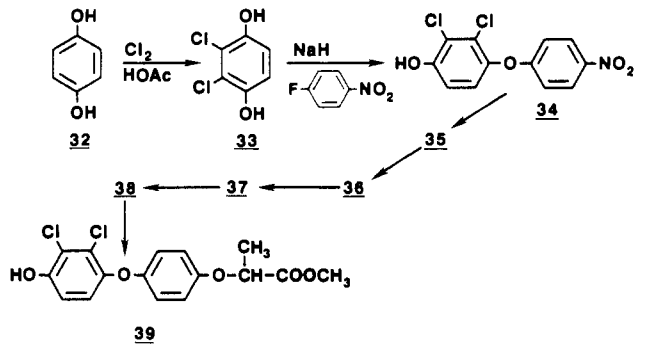
Scheme III



Scheme IV

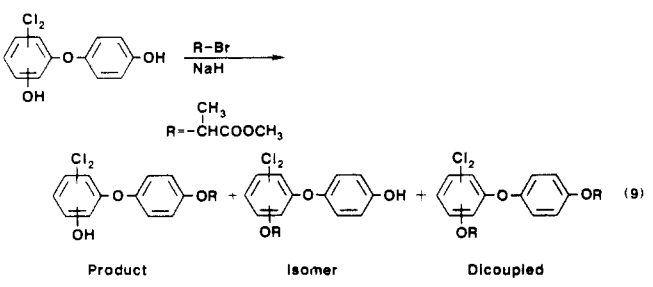


Scheme V



dures in this reaction scheme were the same as those developed for the reactions in Scheme I. Synthesis of **39** (2,3-dichloro-4-hydroxy isomer) was accomplished according to Scheme V. In this scheme, 2,3-dichlorohydroquinone was smoothly prepared according to the method of Conant and Fieser (1923) and subsequent reactions in the scheme were again carried out using the experimental methods developed for Scheme I.

In Schemes I–V, methyl 2-bromopropanoate was coupled with a dihydroxydiphenyl ether in the final reaction as shown in eq 9. Coupling with the hydroxyl group



(9)

on the nonchlorinated ring would afford the desired product, whereas coupling with the hydroxyl group on the chlorinated ring would give the undesired isomer. Finally, if coupling occurred with both hydroxyl groups, an undesired dicoupled product would be obtained. Double coupling would increase the quantity of unreacted dihydroxydiphenyl ether due to depletion of the methyl 2-bromopropanoate. In Table I is given the percent distribution of the desired product, undesired isomer, dicoupled product, dihydroxydiphenyl ether starting material, and reaction byproducts from the final coupling reactions. All coupling reactions were performed under identical conditions, and no attempt was made to optimize reaction yields. From steric considerations, it would appear that the greatest amount of coupling would take place with the unhindered hydroxyl group on the nonchlorinated ring. This was found to be true for all cases as shown in Table I where yields were consistently higher for the product in comparison with the undesired isomer. Where an appreciable amount of undesired isomer was produced, a significant yield of dicoupled product was also obtained. Therefore, when the reactivity of the two hydroxyl groups was competitive, a high yield of product could not be obtained. Only in the synthesis of the 3-OH isomer was it possible to predict that very little coupling would occur with the 3-OH group. This was possible because the 3-OMe group could not be cleaved with boron tribromide–dimethyl sulfide complex; thus, it was clear that the two chlorine atoms ortho to the 3-position sterically hindered the reaction at that position.

Table I. Distribution of Products and Byproducts from the Final Coupling Reaction

		distribution of material, %				
isomer	no.	product	isomer	dicoupled	starting material	unknown byproducts
2,3-dichloro-4-hydroxy	**39**	21	7	24	24	27
2,5-dichloro-4-hydroxy	**31**	18	14	24	25	16
2,4-dichloro-5-hydroxy	7	61	4	1	2	28
2,4-dichloro-3-hydroxy	**16**	76	1	1	5	21
2,4-dichloro-6-hydroxy	**24**	54	5	6	31	8

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Identification of the Isomeric Hydroxylated Metabolites of Methyl 2-[4-(2,4-Dichlorophenoxy)phenoxy]propanoate (Diclofop-Methyl) in Wheat

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The major metabolic pathway for detoxication of diclofop-methyl in tolerant plant species is by ring hydroxylation followed by glucoside conjugation. This investigation reports on the conclusive identification of the three isomeric hydroxylated metabolites of diclofop-methyl obtained from wheat after acid hydrolysis of the glucoside conjugates. Identified as metabolites were the 2,3-dichloro-4-hydroxy, 2,5-dichloro-4-hydroxy, and the 2,4-dichloro-5-hydroxy isomers. The first two metabolites were formed via the NIH shift.

The herbicide diclofop-methyl has been developed for the selective control of undesired grasses (Hoechst AG, 1973). This herbicide also shows considerable promise for the control of wild oat in cereal crops (Miller and Nalawaja, 1974; Friesen et al., 1976). One reason for this herbicidal selectivity may be due to the differences in root growth inhibition that was observed by Shimabukuro et al. (1978). When intact plants are root-treated with diclofop-methyl, root growth of wild oat is severely inhibited while inhibition of wheat root growth is only slight. However, the primary cause for diclofop-methyl selectivity appears to result from the significant differences in the metabolic detoxication pathways of wild oat and wheat (Shimabukuro et al., 1979; Gorecka et al., 1981; Jacobson and Shimabukuro, 1984).

When plants are treated with diclofop methyl, rapid hydrolysis occurs to afford diclofop acid, 2-[4-(2,4-dichlorophenoxy)phenoxy]propanoic acid, in both resistant and susceptible plants. The detoxication of diclofop acid by resistant plants, such as wheat, occurs by hydroxylation of the dichlorophenoxy moiety of diclofop acid (Gorbach et al., 1977; Shimabukuro et al., 1979). This hydroxylated metabolite is rapidly conjugated with glucose; hence, very little hydroxylated diclofop acid in its