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Development of (Phenoxyphenoxy)- and (Benzylphenoxy)propyl Ethers as Potent Insect Juvenile Hormone Mimetics

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We prepared as insect juvenile hormone (JH) mimetics (4-phenoxyphenoxy)- and (4-benzylphenoxy)alkyl ethers in which the oxime moiety of the (4-phenylphenoxy)alkanaldoxime *O*-ether compounds we have already developed is replaced by a simple ether function. The activity against a mosquito, *Culex pipiens*, was examined. Structural factors, especially steric ones, that concern variations in potency were common to the two series of compounds. On the basis of this finding, we optimized the structure as has been done for the earlier oxime compounds, developing 3-(4-benzylphenoxy)propyl and 3-[4-(3-methylphenoxy)phenoxy]propyl isobutyl ethers, the most potent members of the class. The oxygen function was equivalent or somewhat better than the oxime with respect to expression of JH-mimetic activity. A methyl branch at the 2- or 3-positions of the propyl moiety lowered the potency dozens of times, suggesting a disturbance of the steric fitting to the receptor or the taking on of the active conformation.

Based on the receptor map for insect juvenile hormones (JHs) drawn based on results of quantitative structure–activity relationship analysis of the terpenoid 2,4-dodecadienoate JH mimics (Nakayama et al., 1984), we have prepared new classes of terpenoid JH mimics, undecen-2-one oxime *O*-ethers and undecen-2-yl carbamates (Nakayama et al., 1985). The activity of these mimics was comparable to or stronger than that of JH I, methyl (2*E*,6*E*)-*cis*-10,11-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate, against *Culex pipiens* (the common mosquito), *Chilo suppressalis* (the rice-stem borer), and *Musca domestica* (the house fly), but less potent than that of methoprene [isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate], one of the most active JH-mimetic compounds known. To obtain higher activity, we have then transformed the terpenoid structure to a nonterpenoid one within the framework of the receptor map, resulting in the development of the ω-(4-phenoxyphenoxy)- and ω-(4-benzylphenoxy)alkanaldoxime *O*-ether series of JH mimics. The activity against *C. pipiens* of the most active member, 3-[4-(3-methylphenoxy)phenoxy]propionaldoxime *O*-isopropyl ether, exceeded that of methoprene (Niwa et al., 1987).

The structure–activity profile of the new class of compounds is in accord with that of the previous terpenoid oximes. Moreover, the position of the oxime *O*-ether function in a molecule has been found important for high activity, 3-(4-phenoxyphenoxy)- or 3-(4-benzylphenoxy)-propionaldoxime *O*-ethers being dozens of times more potent than the corresponding acetaldoxime *O*-ethers. Recently, propionaldoxime *O*- 2-(4-phenoxyphenoxy)ethyl ethers has been reported, where the oxime function is built in the structure in the reverse of our oxime ethers (Ohsumi et al., 1985). In the same run of assays with our compounds, they were highly active, pI_{50} (M) against *C. pipiens* being 9.50 (Niwa et al., 1987). Previously, the effect of various functions has been examined in the phenoxyphenoxy type of compounds to show that those having a carbamate or ester group are highly active against some species of insects (Karrer and Farooq, 1981). Although the position specificity has not been systematically investigated, it is suggestive that a potent compound is obtainable with a variety of functional groups if they are properly located in the molecule. In this study, we prepared a series of compounds with the simplest functional group, ether, and optimized the structure as has been done for the oxime

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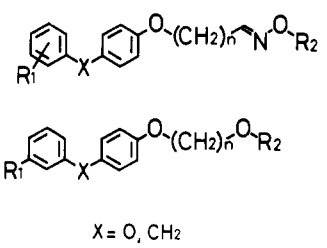


Figure 1. Generic formulas of the previous (phenoxyphenoxy)alkanaldoxime *O*-ether compounds already reported and the new (phenoxyphenoxy)alkyl ether compounds.

compounds. This led us to obtain highly active JH-mimetic compounds 3-(4-benzylphenoxy)propyl and 3-[4-(3-methylphenoxy)phenoxy]propyl isobutyl ethers, the activity against *C. pipiens* being higher than that of methoprene and comparable to or slightly stronger than that of the corresponding propionaldoxime *O*-ethers (Niwa et al., 1987). Figure 1 shows the generic formulas of the previous oximes and the present ether compounds.

EXPERIMENTAL SECTION

^{1}H NMR spectra were obtained in $CDCl_3$ in a JEOL PMX-60 spectrometer with tetramethylsilane as the internal reference. IR spectra were recorded on a Shimadzu IR-27G spectrometer.

2-(4-Phenoxyphenoxy)ethanol. 2-Bromoethanol (1.40 g, 11.2 mmol) was added to 5 mL of water containing 0.36 g (9.00 mmol) of NaOH and 1.0 g (5.38 mmol) of 4-phenoxyphenol. The mixture was stirred for 12 h at room temperature, poured into water, and treated with ether. The ether layer was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness. The crude product was put on a silica gel column that was eluted with 20% ethyl acetate in benzene, giving 0.46 g (37%) of the alcohol as oil: ^{1}H NMR ($CDCl_3$) δ 2.50 (br, 1 H, O*H*), 3.85 (m, 4 H, $C\mathit{H}_2C\mathit{H}_2$).

1-Butoxy-2-(4-phenoxyphenoxy)ethane (1). Sodium hydride (0.08 g, 2.00 mmol, 60% purity) was added to a dimethylformamide solution (5 mL) of 2-(4-phenoxyphenoxy)ethanol (0.20 g, 0.87 mmol). After bubbling was stopped, *n*-butyl bromide (0.17 g, 1.24 mmol) was added to the solution. The mixture was stirred for 4 h at room temperature, poured into water, and treated with *n*-hexane. The *n*-hexane layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 20% *n*-hexane in benzene as solvent, yielding 0.20 g (80%) of 1 as oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, $CH_2C\mathit{H}_3$), 3.51 (t, 2 H, J = 6.5 Hz, $OC\mathit{H}_2CH_2$), 3.72 (t, 2 H, J = 5 Hz, $CH_2C\mathit{H}_2O$), 4.09 (t, 2 H, J = 5 Hz, $ArOC\mathit{H}_2$).

1-(4-Phenoxyphenoxy)-3-propoxypropane (2). By analogy with the preparation of 1, compound **2** was synthesized in 20% yield from *n*-propyl bromide and 3-(4-phenoxyphenoxy)-1-propanol that was prepared from 4-phenoxyphenol and 3-bromo-1-propanol: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, $CH_2C\mathit{H}_3$), 1.55 (m, 2 H, $CH_2C\mathit{H}_2CH_3$), 2.00 (m, 2 H, $CH_2C\mathit{H}_2CH_2$), 3.35 (t, 2 H, J = 7 Hz, $OC\mathit{H}_2CH_2$), 3.57 (t, 2 H, J = 6.5 Hz, $CH_2C\mathit{H}_2O$), 4.00 (t, 2 H, J = 6.5 Hz, $ArOC\mathit{H}_2$).

1-[4-(3-Methylphenoxy)phenoxy]-3-propoxypropane (15). Compound **15** was prepared from *n*-propyl bromide and 3-[4-(3-methylphenoxy)phenoxy]-1-propanol in 67% yield by analogy with the preparation of 1: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 7 Hz, $CH_2C\mathit{H}_3$), 1.55 (m, 2 H, $CH_2C\mathit{H}_2CH_2$), 2.00 (m, 2 H, $CH_2C\mathit{H}_2CH_2$), 2.27 (s, 3 H, $ArC\mathit{H}_3$), 3.35 (t, 2 H, J = 6.5 Hz, $OC\mathit{H}_2CH_2$), 3.64 (t, 2 H, J = 6.5 Hz, $CH_2C\mathit{H}_2O$), 4.00 (t, 2 H, J = 6.5 Hz, $ArOC\mathit{H}_2$). The propanol was produced from 4-(3-methylphenoxy)-phenol and 3-bromo-1-propanol in tetrahydrofuran in the presence of *t*-BuOK.

1-(4-Benzylphenoxy)-2-butoxyethane (18). By analogy with the preparation of 1, compound **18** was prepared by the reaction of *n*-butyl iodide and 1-(4-benzylphenoxy)ethanol in dimethyl sulfoxide in the presence of *t*-BuOK with a 17% yield: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 7 Hz, $CH_2C\mathit{H}_3$), 3.48 (t, 2 H, J = 7 Hz, $OC\mathit{H}_2CH_2$), 3.70 (t, 2 H, J = 5 Hz, $CH_2C\mathit{H}_2O$), 3.88 (s, 2 H, $ArCH_2Ar$), 4.04 (t, 2 H, J = 5 Hz, $ArOC\mathit{H}_2$). The alcohol was produced by a reaction between 4-benzylphenol and 2-bromoethanol in dimethyl sulfoxide in the presence of KOH.

1-(4-Benzylphenoxy)-3-propoxypropane (19). Compound **19** was prepared by analogy with the preparation of **18** from propyl iodide and 1-(4-benzylphenoxy)-3-propanol in 22% yield: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz, $CH_2C\mathit{H}_3$), 1.55 (m, 2 H, $CH_2C\mathit{H}_2CH_3$), 1.99 (m, 2 H, $CH_2C\mathit{H}_2CH_2$), 3.32 (t, 2 H, J = 6 Hz, $OC\mathit{H}_2CH_2$), 3.52 (t, 2 H, J = 6 Hz, $CH_2C\mathit{H}_2O$), 3.88 (s, 2 H, $ArC\mathit{H}_2Ar$), 3.98 (t, 2 H, J = 6 Hz, $ArOC\mathit{H}_2$). The propanol was produced by the reaction of 4-benzylphenol and 3-bromo-1-propanol in dimethyl sulfoxide in the presence of KOH.

1-(4-Benzylphenoxy)-3-isobutoxypropane (20). Compound **20** was prepared in 10% yield by analogy with the preparation of **19** by the reaction of isobutyl bromide with 3-(benzylphenoxy)-1-propanol in dimethylformamide, with NaH as base: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 7 Hz, $CH(C\mathit{H}_3)_2$), 1.97 (m, 2 H, $CH_2C\mathit{H}_2CH_2$), 3.12 (d, 2 H, J = 6.5 Hz, $OC\mathit{H}_2CH$), 3.50 (t, 2 H, J = 6.5 Hz, $CH_2C\mathit{H}_2O$), 3.88 (s, 2 H, $ArC\mathit{H}_2Ar$), 3.99 (t, 2 H, J = 6.5 Hz, $ArOC\mathit{H}_2$).

3-(4-Phenoxyphenoxy)-1-propoxybutane (13). Compound **13** was prepared from *n*-propyl bromide and 3-(4-phenoxyphenoxy)-1-butanol in 23% yield by analogy with the preparation of 1: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, $CH_2C\mathit{H}_3$), 1.28 (d, 3 H, J = 6.5 Hz, $CHC\mathit{H}_3$), 3.30 (t, 2 H, J = 6.5 Hz, $OC\mathit{H}_2CH_2$), 3.50 (t, 2 H, J = 6 Hz, $CH_2C\mathit{H}_2O$), 4.45 (m, 1 H, $ArOC\mathit{H}$). The butanol was synthesized by a reaction between 4-phenoxyphenol and 3-bromo-1-butanol (Walling et al., 1939) in hexamethylphosphoric triamide in the presence of *t*-BuOK.

3-(4-Phenoxyphenoxy)-1-isobutoxybutane (14). Compound **14** was prepared in 21% yield by the same method as described for the preparation of **13**, with isobutyl bromide used instead of *n*-propyl bromide: ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 6 H, J = 6.5 Hz, $CH(C\mathit{H}_3)_2$), 1.29 (d, 3 H, J = 6.5 Hz, $CHC\mathit{H}_3$), 3.13 (d, 2 H, J = 6.5 Hz, $OC\mathit{H}_2CH$), 3.52 (t, 2 H, J = 6.5 Hz, $CH_2C\mathit{H}_2O$), 3.48 (m, 1 H, $ArOC\mathit{H}$).

3-(4-Phenoxyphenoxy)propyl Chloride. Potassium *tert*-butoxide (2.00 g, 17.9 mmol) and 1-bromo-3-chloropropane (3.80 g, 24.1 mmol) were added to a tetrahydrofuran solution (20 mL) of 4-phenoxyphenol (3.00 g, 16.1 mmol). After being stirred for 3 h at refluxing temperature, the mixture was diluted with water and extracted with *n*-hexane. The extract was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure, yielding an oily product. The chloride was used for later reactions without further purification.

1-Isobutoxy-3-(4-phenoxyphenoxy)propane (7). 3-(4-Phenoxyphenoxy)propyl chloride (0.40 g, 15.2 mmol) was added to 10 mL of isobutyl alcohol in which 0.15 g (6.5 mmol) of sodium metal had been dissolved. The mixture was stirred for 24 h at 90 °C, poured into water, and treated with *n*-hexane. The *n*-hexane layer was washed with water, dried over $MgSO_4$, and concentrated under

reduced pressure to dryness. The residual oil was purified by silica gel column chromatography with 50% *n*-hexane in benzene as solvent, to give 0.26 g (55%) of oily **7**: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 6.5 Hz, $CH(CH_3)_2$), 2.00 (m, 2 H, $CH_2CH_2CH_2$), 3.17 (d, 2 H, J = 6.5 Hz, OCH_2CH), 3.55 (t, 2 H, J = 6 Hz, CH_2CH_2O), 4.03 (t, 2 H, J = 6.5 Hz, $ArOCH_2$).

1-(Allyloxy)-3-(4-phenoxyphenoxy)propane (5). Compound **5** was prepared by analogy with the preparation of **7** in 45% yield by the use of allyl alcohol: ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 2 H, $CH_2CH_2CH_2$), 3.59 (t, 2 H, J = 6 Hz, CH_2CH_2O), 4.00 (m, 4 H, $OCH_2CH=$ and $ArOCH_2$), 5.25 (m, 2 H, $CH=CH_2$), 5.80 (m, 1 H, $CH_2CH=CH_2$).

1-(4-Phenoxyphenoxy)-3-(propargyloxy)propane (6). Compound **6** was prepared by analogy with the preparation of **7** in 29% yield by the use of propargyl alcohol: ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 2 H, $CH_2CH_2CH_2$), 2.48 (t, 1 H, J = 2 Hz, $C\equiv CH$), 3.64 (t, 2 H, J = 6.5 Hz, CH_2CH_2O), 4.00 (t, 2 H, J = 6.5 Hz, $ArOCH_2$), 4.10 (t, 2 H, J = 2 Hz, $OCH_2C\equiv$).

1-*sec*-Butoxy-3-(4-phenoxyphenoxy)propane (8). Compound **8** was prepared by analogy with the preparation of **7** in 29% yield by the use of *sec*-butyl alcohol and triethylamine as base: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.08 (d, 3 H, J = 6 Hz, $CHCH_3$), 1.40 (m, 2 H, $CHCH_2CH_3$), 1.97 (m, 2 H, $CH_2CH_2CH_2$), 3.25 (m, 1 H, OCH), 3.52 (t, 2 H, J = 6 Hz, CH_2CH_2O), 3.98 (t, 2 H, J = 6 Hz, $ArOCH_2$).

1-Ethoxy-4-(4-phenoxyphenoxy)butane (3). Compound **3** was prepared from ethanol and 4-(4-phenoxyphenoxy)butyl bromide in 49% yield by analogy with the preparation of **7**: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 3.90 (t, 2 H, J = 5.5 Hz, $ArOCH_2$). The bromide was synthesized by a reaction between 1,4-dibromobutane and 4-phenoxyphenol.

1-Methoxy-5-(4-phenoxyphenoxy)pentane (4). Compound **4** was prepared from methanol and 5-(4-phenoxyphenoxy)pentyl bromide in 64% yield by analogy with the preparation of **3**: ^{1}H NMR ($CDCl_3$) δ 3.28 (s, 3 H, OCH_3), 3.34 (t, 2 H, J = 6 Hz, CH_2CH_2O), 3.88 (t, 2 H, J = 6 Hz, $ArOCH_2$).

2-Methyl-1-(4-phenoxyphenoxy)-3-propoxypropane (11). Compund **11** was prepared in 14% yield by analogy with the preparation of **7** from 2-methyl-3-(4-phenoxyphenoxy)propyl chloride and propoxide prepared from 1-propanol and NaH: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.08 (d, 3 H, J = 6 Hz, $CHCH_3$), 1.55 (m, 2 H, $CH_2CH_2CH_3$), 2.22 (m, 1 H, CH), 3.34 (t, 2 H, J = 6.5 Hz, OCH_2CH_2), 3.41 (d, 2 H, J = 6.5 Hz, $CHCH_2O$), 3.88 (m, 2 H, $ArOCH_2$). The chloride was synthesized by the reaction of 1-bromo-3-chloro-2-methylpropane with 4-phenoxyphenol in tetrahydrofuran in the presence of *t*-BuOK.

1-Isobutyl-2-methyl-3-(4-phenoxyphenoxy)propane (12). Compound **12** was prepared by analogy with the preparation of **11** in 60% yield by the use of isobutyl alcohol: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 7 Hz, $CH(CH_3)_2$), 1.06 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.14 (d, 2 H, J = 6 Hz, OCH_2CH), 3.38 (d, 2 H, J = 6 Hz, $CHCH_2O$), 3.90 (m, 2 H, $ArOCH_2$).

1-Isobutyl-3-[4-(3-methylphenoxy)phenoxy]propane (16). Compound **16** was prepared from 3-[4-(3-methylphenoxy)phenoxy]propyl chloride and isobutyl alcohol in 36% yield by analogy with the preparation of **4**: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 6 Hz, $CH(CH_3)_2$), 1.70 (m, 1 H, CH), 1.97 (m, 2 H, $CH_2CH_2CH_2$), 2.33 (s, 3 H, $ArCH_3$), 3.12 (d, 2 H, J = 6.5 Hz, OCH_2CH) 3.51 (t, 2 H, J = 6.5 Hz, CH_2CH_2O), 3.98 (t, 2 H, J = 6.5 Hz, $ArOCH_2$). The chloride was synthesized from 4-(3-methylphenoxy)phenol (Niwa et al., 1987) and 1-bromo-3-chloropropane.

1-[4-(3-Methylphenoxy)phenoxy]-3-(neopentyloxy)propane (17). Compound **17** was prepared by analogy with the preparation of **16** in 22% yield by the use of neopentyl alcohol: ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9 H, $C(CH_3)_3$), 2.02 (m, 2 H, $CH_2CH_2CH_2$), 2.27 (s, 3 H, $ArCH_3$), 3.05 (s, 2 H, OCH_2C), 3.56 (t, 2 H, J = 6 Hz, CH_2CH_2O) 4.01 (t, 2 H, J = 6.5 Hz, $ArOCH_2$).

1-(4-Benzylphenoxy)-2-phenoxyethane (22), -3-phenoxypropane (23), and -4-phenoxybutane (24). 4-Benzylphenol and the appropriate phenoxyalkyl bromide were reacted in dimethyl sulfoxide in the presence of KOH by a method analogous with the preparation of 3-(4-phenoxyphenoxy)propyl chloride described above. **22**: yield 47%; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 2 H, $ArCH_2Ar$), 4.24 (s, 4 H, OCH_2CH_2O). **23**: yield 86%; ^{1}H NMR ($CDCl_3$) δ 2.15 (m, 2 H, $CH_2CH_2CH_2$), 3.85 (s, 2 H, $ArCH_2Ar$), 4.05 (t, 4 H, J = 6 Hz, $ArOCH_2$). **24**: yield 85%; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 2 H, $ArCH_2Ar$), 3.98 (t, 4 H, J = 6 Hz, $ArOCH_2$).

1-(4-Benzylphenoxy)heptane (25) and 2-[2-(4-Benzylphenoxy)ethyl]-1,3-dioxane (21). 4-Benzylphenol was reacted with *n*-heptyl bromide and 2-(2-bromoethyl)-1,3-dioxane to give **21** (82%) [^{1}H NMR ($CDCl_3$) δ 4.72 (t, 1 H, J = 5.5 Hz, CH)] and **25** (84%) [^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 6 Hz, CH_2CH_3), 3.86 (t, 2 H, J = 6 Hz, $ArOCH_2$), 3.86 (s, 2 H, $ArCH_2Ar$)], respectively, by analogy with the preparation of **22–24**.

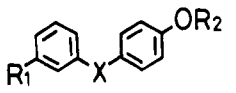
4-(4-Phenoxyphenoxy)-1-butene. 4-Bromo-1-butene (1.20 g, 8.89 mmol) and *t*-BuOK (0.90 g, 8.5 mmol) were added to a tetrahydrofuran solution (10 mL) of 4-phenoxyphenol (1.50 g, 8.06 mmol). The mixture was stirred for 2 days at refluxing temperature, poured into water, and treated with *n*-hexane. The *n*-hexane layer was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness to yield an oily product. This compound was used for later reactions without further purification.

1-(4-Phenoxyphenoxy)-3-propoxybutane (9). Mercuric acetate (0.48 g, 1.51 mmol) suspended in 10 mL of 1-propanol was added to 15 mL of 1-propanol containing 0.35 g (1.46 mmol) of 4-(4-phenoxyphenoxy)-1-butene. After being stirred for 1 h at room temperature, KOH (0.30 g) and $NaBH_4$ (0.03 g, 0.8 mmol) were added to the mixture, which was then stirred for 30 min at room temperature, diluted with water, and extracted with *n*-hexane. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The oily residue was put on a silica gel column that was eluted with 30% *n*-hexane in benzene, to give 0.09 g (12%) of oily **9**: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.18 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 4.00 (t, 2 H, J = 6.5 Hz, $ArOCH_2$).

3-Isobutoxy-1-(4-phenoxyphenoxy)butane (10). Compound **10** was prepared in 18% yield from isobutyl alcohol, mercuric acetate, and 4-(4-phenoxyphenoxy)-1-butene by analogy with the preparation of **9**: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 6.5 Hz, $CH(CH_3)_2$), 1.18 (d, 3 H, J = 6 Hz, $CHCH_3$), 4.02 (t, 2 H, J = 6 Hz, $ArOCH_2$).

All of the final products listed in Table I are either oil or glass at room temperature. The identification of the molecular formulas was made by elemental analyses for C and H within the error of ±0.3%. The extraction and chromatography with use of benzene as solvent were done in a well-ventilated hood. In consideration of the toxicity and carcinogenicity of benzene, it could be replaced by less toxic toluene or ethyl acetate in the extraction and the chromatography.

Table I. Structure and Activity of (4-Phenoxyphenoxy)- and (4-Benzylphenoxy)alkyl Ethers



compd	R_1	X	R_2	pI_{50}
1	H	O	$CH_2CH_2OCH_2CH_2CH_2CH_3$	8.08
2	H	O	$CH_2CH_2CH_2OCH_2CH_2CH_3$	9.47
3	H	O	$CH_2CH_2CH_2CH_2OCH_2CH_3$	7.93
4	H	O	$CH_2CH_2CH_2CH_2CH_2OCH_3$	6.42
5	H	O	$CH_2CH_2CH_2OCH_2CH{=}CH_2$	9.07
6	H	O	$CH_2CH_2CH_2OCH_2C{\equiv}CH$	9.01
7	H	O	$CH_2CH_2CH_2OCH_2CH(CH_3)_2$	9.73
8	H	O	$CH_2CH_2CH_2OCH(CH_3)CH_2CH_3$	8.90
9	H	O	$CH_2CH_2CH(CH_3)OCH_2CH_2CH_3$	9.60
10	H	O	$CH_2CH_2CH(CH_3)OCH_2CH(CH_3)_2$	9.68
11	H	O	$CH_2CH(CH_3)CH_2OCH_2CH_2CH_3$	8.30
12	H	O	$CH_2CH(CH_3)CH_2OCH_2CH(CH_3)_2$	8.42
13	H	O	$CH_2CHCH_2CH_2OCH_2CH_2CH_3$	8.21
14	H	O	$CH_2CHCH_2CH_2OCH_2CH(CH_3)_2$	8.08
15	Me	O	$CH_2CH_2CH_2OCH_2CH_2CH_3$	9.72
16	Me	O	$CH_2CH_2CH_2OCH_2CH(CH_3)_2$	10.49
17	Me	O	$CH_2CH_2CH_2OCH_2C(CH_3)_3$	10.28
18	H	CH_2	$CH_2CH_2OCH_2CH_2CH_2CH_3$	8.07
19	H	CH_2	$CH_2CH_2CH_2OCH_2CH_2CH_3$	9.18
20	H	CH_2	$CH_2CH_2CH_2OCH_2CH(CH_3)_2$	9.37
21	H	CH_2	$CH_2CH_2CH(OCH_2)_2CH_2$	7.19
22	H	CH_2	CH_2CH_2OPh	6.66
23	H	CH_2	$CH_2CH_2CH_2OPh$	7.88
24	H	CH_2	$CH_2CH_2CH_2CH_2OPh$	6.09
25	H	CH_2	$CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	7.17
JH I				6.29
methoprene				9.50

Bioassay Procedure. Fourth larval instars of *C. pipiens pallens* Coquillet were selected from colonies maintained at 28 °C in water that contained a feed mixture of mouse food and dry yeast. The eggs were a gift of the Sumitomo Chemical Co., Ltd. Three batches of 20 larvae each were transferred to disposable plastic tumblers containing 100 mL of water. An ethanol solution (10 μL) of the test compounds then was added to the tumblers, after which the diet powder was added. The tumblers were covered with transparent plastic cups to prevent the adults from flying away. After 7 days at 28 °C, the results were scored as the percentage of unemerged adults, including those that could escape only partly from the pupal cuticles. The experimental results in the bioassays were confirmed mostly by replication at concentrations at which high ratings (usually more than 50% inhibition of metamorphosis) were recorded, but experiments usually were not repeated at concentrations recorded for lower activity. When an abnormal rating was found, repetitions were made at that concentration and those nearby. When more than one abnormal rating was obtained, the experiment was repeated for the entire concentration range. All the data, excluding the abnormal value, were averaged. The nonemergence percentage of the control (no chemicals added except 10 μL of ethanol) was less than 10% through the runs of the experiments.

The activity was expressed in terms of pI_{50} (M), the logarithm of the reciprocal of the concentration at which 50% inhibition of metamorphosis is observed. The data are summarized in Table I, together with those of JH I and methoprene as references. JH I was purchased from Sigma Chemical Co., and methoprene was provided by Earth Chemical Co. Ltd.

RESULTS AND DISCUSSION

Synthesis of Compounds. Reaction of 2-bromoethanol with 4-phenoxyphenol in aqueous NaOH produced 2-(4-phenoxyphenoxy)ethanol. This compound gave compound 1 by the reaction with *n*-butyl bromide in dimethylformamide in the presence of NaH. Similarly, compound **2** was prepared via 3-(4-phenoxyphenoxy)-1-propanol. Compound **15** was synthesized by essentially the same process but starting from 4-(3-methylphenoxy)phenol, and compounds **18–20** were prepared starting from 4-benzylphenol. The methyl and ethyl ethers **3** and **4** were produced by a reaction between the appropriate alkoxide and ω-(4-phenoxyphenoxy)alkyl bromide that was prepared from the appropriate dibromoalkane and 4-phenoxyphenol. 3-(Phenoxyphenoxy)- and 3-[4-(3-methylphenoxy)phenoxy]propyl chlorides similarly prepared gave compounds **5–8**, **16**, and **17** by reaction with the appropriate alcohol in the presence of a base. These processes are summarized in Scheme I.

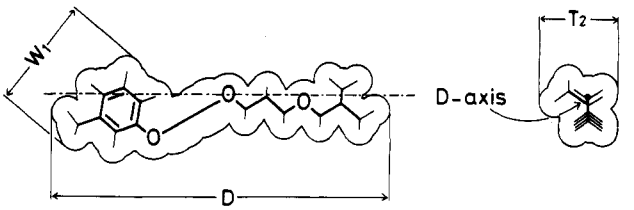


Figure 2. Definition of dimensional parameters. The model compound is 3-[4-(3-methylphenoxy)phenoxy]propyl isobutyl ether (**16**), and the line drawn between the two aryl oxygen atoms represents the central benzene moiety located perpendicularly to the page plane. The ends of the bars of the structure represent hydrogen atoms.

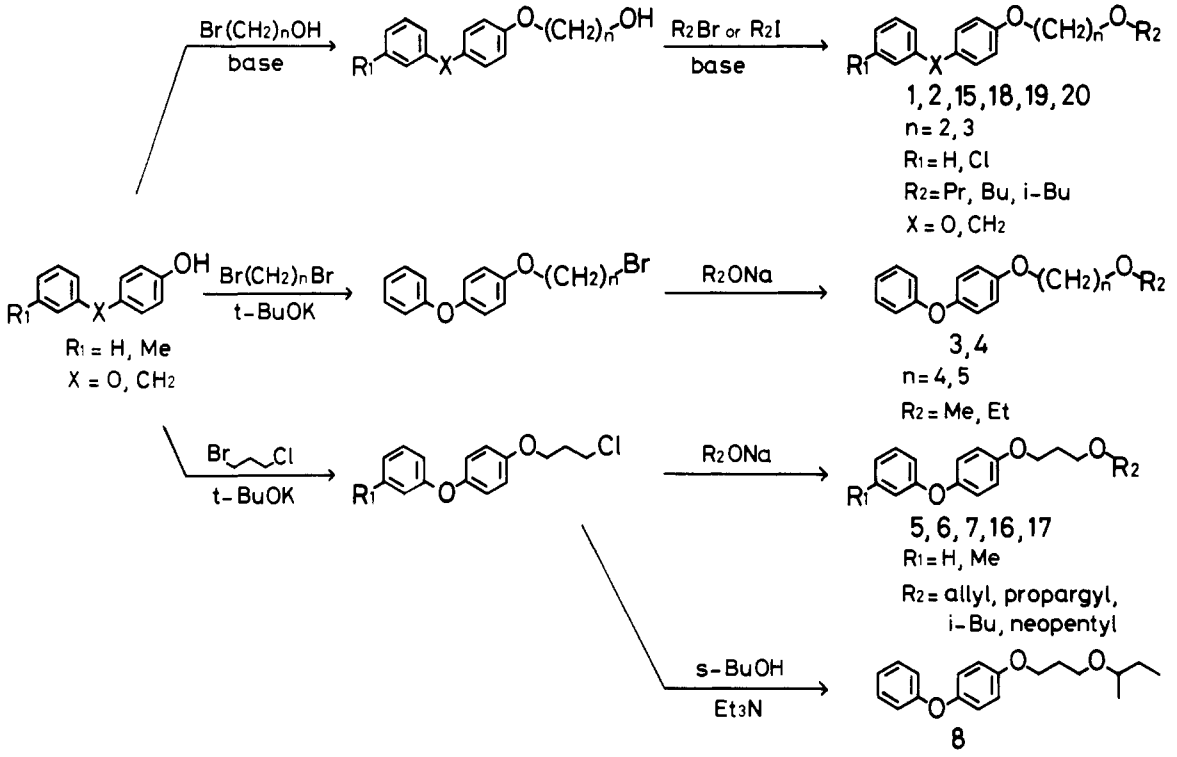
Reaction of 4-bromo-1-butene with 4-phenoxyphenol in the presence of *t*-BuOK to gave 4-(4-phenoxyphenoxy)-1-butene, from which the branched ethers **9** and **10** were prepared by alkoxy mercuration–demercuration (Wakabayashi, 1969). Compounds **11** and **12** were prepared from 2-methyl-3-(4-phenoxyphenoxy)propyl chloride and the appropriate alkoxide, and **13** and **14** were prepared in the reverse way from 3-(4-phenoxyphenoxy)-1-butanol and the appropriate alkyl bromide. The intermediate propyl chloride and butanol were synthesized conventionally, as shown in Scheme II. Compounds **21–25** were prepared by O-alkylation of 4-benzylphenol by the appropriate alkyl bromide under basic conditions.

These compounds are listed in Table I, together with their activity data.

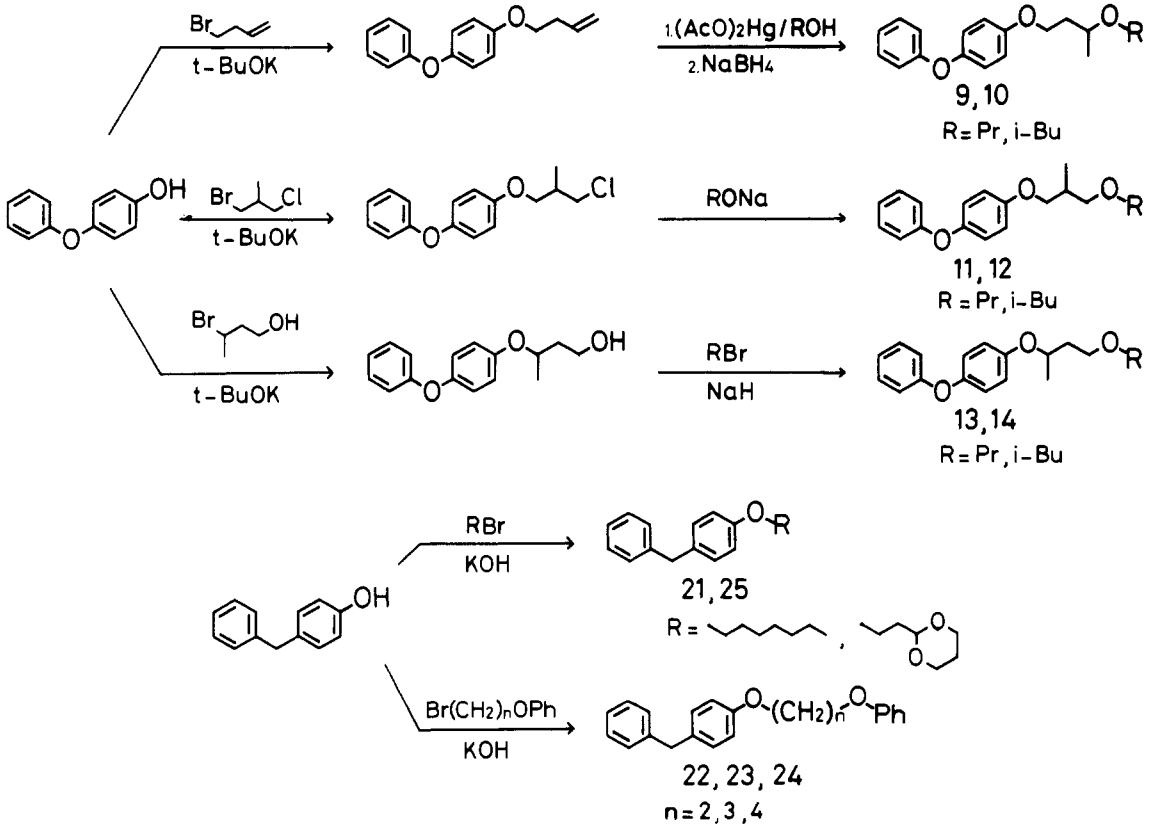
Design and Structure–Activity Relationship. Most of the compounds listed in Table I were prepared so as to satisfy the optimum molecular length *D* for activity, about 21 Å, suggested in our previous reports (Nakayama et al., 1984, 1985; Niwa et al., 1987). This length is measured along the *D*-axis, which passes on the phenoxy oxygen atom attached to the alkyl chain with the angle of 40.02° to the connecting bond. The definition was made for the fully extended conformation shown in Figure 2 and in consideration of the correspondence between this and earlier series of compounds. The molecule is drawn so that the angle between the two benzene rings becomes 90°, at which the mutual overlap of the van der Waals radii becomes least significant between ortho substituents. The calculation was made with a computer program devised for the estimation of *D* and related dimensional parameters (Asao and Iwamura, unpublished results).

Within the length condition described above (*D* being about 21 Å), we prepared phenoxyphenoxy compounds **1–4** and benzylphenoxy compounds **18** and **19** first to examine the positional effect on activity of the oxygen function at the ether end. The result was that the propyl propyl ethers (**2** and **19**) were the most potent in each series. An electronic or hydrophilic interaction probably operates most effectively between the compound and receptor when the

Scheme I



Scheme II



oxygen function is built in at the δ-position from the phenoxy oxygen atom. A similar effect was observed for (benzylphenoxy)alkyl phenyl ethers **22–24**. Compound **23** has the function at the correct position, has a total length (20.2 Å) nearest to the optimum, and thus has the highest activity of the three, the *D* values of **22** and **24** being 19.4 and 21.9 Å, respectively. The oxygen function is in the desired place in the trimethylenedioxy compound **21**, but its *D* (18.6 Å) is significantly shorter than the optimum. Compound **25**, which lacks the ether structure, had lower but not negligible activity, about 10 times as high as that of JH I. This probably shows that the overall structural shape is another factor of basic importance for activity (Nakayama et al., 1984). In this respect, there have been reported a number of terpenoid compounds having a phenoxy end. Their activity varies depending on the

lengths of both the terpenoid moiety and aromatic group (Henrick, 1982), and this may be at least partly attributed to the positional effect of the phenoxy oxygen atom.

On the basis of these results, we decided to prepare only compounds of the propyl ether type. A methyl branch at the 2- or 3-position of the central trimethylene chain lowered the potency, as seen with compounds **11–14**, but such a branch at the 1-position was not detrimental to the activity (compounds **9** and **10**). The protuberance at 2- and 3-positions may disturb the steric fitting of the molecule to the receptor or obstruct the taking on of the conformation needed for accommodation to the receptor.

In our study of alkanaldoxime *O*-ethers (Nakayama et al., 1985; Niwa et al., 1987), we found that the bulkiness arising from a branch or cyclization at the alkyl end is concerned with variations in activity. Bulkiness is reflected in the steric parameter T_2, the thickness in the vertical direction to the zigzag, skeletal chain as indicated in Figure 2. Its optimum has been estimated to be about 5 Å from the result of the analysis of the quantitative structure–activity relationship of the oxime compounds and is satisfied only by a methyl branch (T_2 being 5.05 Å). Coincidentally, the present compounds with isobutyl at the alkyl end had within experimental error a few to several times higher activity than the nonbranched congeners. Moreover, there is an optimum condition, about 7 Å, for the whole width W_1 shown in Figure 2 of the benzene end. We thus, prepared 3-(4-benzylphenoxy)propyl isobutyl ether (**20**) (D, W_1, and T_2 being 20.8, 6.23, and 5.05 Å, respectively) and 3-[4-(3-methylphenoxy)phenoxy]propyl isobutyl ether (**16**) (D, W_1, and T_2 being 21.7, 7.18, and 5.05 Å, respectively). The activity against *C. pipiens* was excellent as expected, being several to ten times that of methoprene.

The results of this study show that the structural features operative at the two ends of the molecule are common to this series of compounds and the previous (4-phenoxyphenoxy)- and (4-benzylphenoxy)alkanaldoxime *O*-ethers and that the oxime and oxygen functions are equivalent with respect to the expression of JH-mimetic activity. The structurall information obtained in this study, together with those obtained earlier, should help in the development of further active structures.

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Supplementary Material Available: Table of analytical data for (4-phenoxyphenoxy)- and (4-benzylphenoxy)alkyl ethers (1 page). Ordering information is given on any current masthead page.

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Development of (4-Alkoxyphenoxy)- and (4-Alkylphenoxy)alkanaldoxime *O*-Ethers as Potent Insect Juvenile Hormone Mimics and Their Structure–Activity Relationships

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We prepared insect juvenile hormone (JH) mimetic (4-alkoxyphenoxy)- and (4-alkylphenoxy)alkanaldoxime *O*-ethers in which the 4-phenoxy moiety of the (4-phenoxyphenoxy)alkanaldoxime *O*-ether type of compounds we have previously developed was replaced by an alkoxy or alkyl. The activity of the most active members against the mosquito (*Culex pipiens*) was as high as or slightly higher than that of the compounds known so far as the most active of JH mimics. An equation for the structure–activity relationship of this class of compounds was formulated to understand the potency in terms of the structural factors.

In our studies of the development of new insect juvenile hormone (JH) mimics, we have prepared (phenoxyphenoxy)- and (benzylphenoxy)propionaldoxime *O*-isopropyl ether-type compounds (Nakayama et al., 1985; Niwa et al., 1988). The results have taught us that the dimensional features of the phenoxy end of the molecule are important for activity, as is the position of the oxime function in the molecule. In this study, the terminal phenyl ether moiety

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