Insect Juvenile Hormone Mimetic Activity of (4-Substituted)phenoxyalkyl Compounds with Various Nitrogenous and Oxygenous Functions and Its Relationship to Their Electrostatic and Stereochemical Properties

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We prepared classes of insect juvenile hormone (JH) mimetic compounds in which oxime, hydroxylamine, ester, amide, carbamate, and urea were built in at the alkane moiety of the 4-substituted phenyl alkyl ether structure. Some of them had effects on *Culex pipiens* as strong as those of the most active JH mimetics known. Calculation of the electrostatic potentials and stereochemical interpretations showed that the most active compound of each class was the entity in which the function in question was incorporated so that its negative potential peak was about 4.6 Å distant from the molecular edge within the framework of the receptor model drawn previously by us. The potency of α,β-unsaturated esters was anomalously high when compared with that of the corresponding saturated esters, irrespective of the fact that both esters equally satisfy the electrostatic and stereochemical conditions. The reactivity properties of the unsaturated esters showed that this structure made the molecules resistant to hydrolysis, suggesting that the α,β-unsaturated esters, like natural JHs and methoprene, owe much of their effect to this property.

Compounds with insect juvenile hormone (JH) activity have a variety of functional groups at one end of the molecule, ranging from single atoms like that in ether (Niwa et al., 1989) and in amine (Wright and Sonnet, 1973; Niwa et al., 1990) to rather complex ester (Röller et al., 1967; Henrick et al., 1982), amide (Cruickshank and Palmere, 1971), carbamate (Wright and Schwartz, 1972; Nakayama et al., 1985), oxime (Niwa et al., 1988; Hayashi et al., 1989), and even aromatic groups (Bowers, 1969; Karrer and Farooq, 1981; Hayashi et al., 1990a). Nonaromatic ester, carbamate, and oxime functions and aromatic phenyl, phenoxy, and pyridyloxy functions found in active JH mimetics all have negative electrostatic potentials extended in a certain direction (Hayashi et al., 1990b). The stereochemical interpretations made on the basis of such findings have suggested that the most active members of the classes of compounds with these functions are entities with dimensions that fit into the receptor cavity well; such compounds have an electrostatic potential peak that comes on a specific site of the receptor surface.

We prepared classes of JH mimetic compounds with a variety of nonaromatic functions incorporated at one end of 4-alkyl- and 4-alkoxyphenyl alkyl ether structures. The compounds with a negative potential peak that hits the specific site had the highest potency in each class, and some of them had as much JH mimetic activity as methoprene [isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate]. The potency of simple esters was anomalously low in view of their electrostatic and stereochemical features, but α,β-unsaturated congeners had high potency. An investigation of their reactivity properties showed that the unsaturated structure makes the molecules resistant to hydrolysis, and this led us to think that the α,β-unsaturated ester compounds, like natural JHs and methoprene which is highly active, owe much of their potency to this feature. Figure 1 shows the general formula of the compounds prepared and studied.

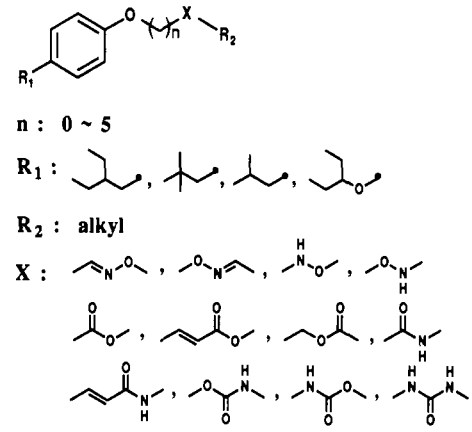

Figure 1. Generic formula of JH active compounds prepared and studied.

EXPERIMENTAL PROCEDURES

Synthesis. ^{1}H NMR spectra were obtained in $CDCl_3$ on a JEOL 60 spectrometer with tetramethylsilane as the internal reference.

Compounds **2d** and **5a–d** have been reported elsewhere (Hayashi et al., 1989).

4-Isobutyrylanisole. Anisole (28 g, 0.26 mol) was added slowly to a mixture of CH_2Cl_2 (100 mL) and anhydrous $AlCl_3$ (38 g, 0.28 mol). Isobutyryl chloride (25 g, 0.23 mol) was then added to the mixture at below 0 °C in an ice–salt bath. The mixture was stirred for 4 h at room temperature and poured into ice–water (100 g) to which 81 mL of concentrated HCl had been added. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving 48 g (92%) of the crude anisole.

4-Isobutyrylphenol. A mixture of 4-isobutyrylanisole (48 g, 0.28 mol) and pyridine hydrochloride (150 g, 1.30 mol) was heated for 10 h at 180 °C with stirring. The mixture was cooled, poured into water, and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving 47 g of the phenol.

4-Isobutylphenol. A mixture of mossy zinc (70 g), mercuric chloride (7 g), water (100 mL), and concentrated HCl (3.5 mL) was shaken for 5 min and decanted. To the amalgamated zinc

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were added water (30 mL), concentrated HCl (80 mL), toluene (60 mL), and 4-isobutyrylphenol (47 g, 0.29 mol), and the reaction mixture was boiled vigorously for 10 h during which time three 10-mL portions of concentrated HCl were added at approximately 3-h intervals. After the mixture was cooled to room temperature, the toluene layer was removed, and the remaining aqueous layer was extracted with toluene. The organic layers were combined, washed with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was distilled at 99 °C/6 mmHg to yield 18 g (51% from isobutyryl chloride) of the phenol.

By an analogous method, 4-(2-ethylbutyl)phenol and 4-neopentylphenol were prepared from 2-ethylbutyryl chloride and 2,2-dimethylpropionyl chloride, respectively, in place of the isobutyryl chloride.

4-(1-Ethylpropoxy)phenol. 3-Bromopentane (1.4 g, 9 mmol) was added slowly to a dimethyl sulfoxide (Me_2SO) solution (30 mL) of hydroquinone (1.5 g, 14 mmol) and powdered KOH (1.4 g, 21 mmol, 85% purity). The mixture was stirred for 4 h at 50–60 °C, poured into water, and extracted with ethyl acetate. The ethyl acetate layer was extracted with 1 N NaOH, and the aqueous layer was acidified by concentrated HCl and extracted with diethyl ether. The diethyl ether extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give 0.71 g (43%) of the oily phenol.

4-(2-Ethylbutyl)phenoxypropionaldehyde Diethyl Acetal. To a Me_2SO solution (5 mL) of 4-(2-ethylbutyl)phenol (1.0 g, 5.6 mmol) and powdered KOH (0.48 g, 7.3 mmol, 85% purity) was added chloropropionaldehyde diethyl acetal (1.22 g, 7.3 mmol). The mixture was stirred for 2 h at 50–60 °C, poured into water, and extracted with *n*-hexane. The extract was washed with water, dried over $MgSO_4$, and freed of solvent under reduced pressure, giving 1.72 g (99%) of the acetal.

4-(2-Ethylbutyl)phenoxypropionaldoxime *O*-Ethyl Ether (3a). To an ethanol solution of 4-(2-ethylbutyl)phenoxypropionaldehyde diethyl acetal (1.72 g, 5.6 mmol) was added *O*-ethylhydroxylamine hydrochloride (0.71 g, 7.3 mmol), 6 N HCl (0.2 mL), and water. The mixture was stirred for 12 h at 50–60 °C, poured into water, and extracted with *n*-hexane. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 10% ethyl acetate in *n*-hexane, yielding 1.07 g (69%) of the oxime *O*-ether **3a**: ^{1}H NMR ($CDCl_3$) δ 7.43 (t, 1 H, J = 6 Hz, C*H*N), 6.86 (m, 4 H, Ar*H*), 4.10 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.03 (t, 2 H, J = 6 Hz, Ar OCH_2), 2.70 (m, 2 H, Ar OCH_2CH_2), 2.47 (d, 2 H, J = 6 Hz, Ar CH_2), 1.27 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.25 [m, 5 H, $CH(CH_2)_2$], 0.85 (t, 6 H, J = 6 Hz, $2CH_3$).

The oxime *O*-ethers **2a–c** and **3a–d** were prepared according to the method of Hayashi et al. (1989).

4-(2-Ethylbutyl)phenoxybutyronitrile. 4-Chlorobutyronitrile (0.72 g, 7.0 mmol) was added slowly to a Me_2SO solution (5 mL) of 4-(2-ethylbutyl)phenol (1.0 g, 5.6 mmol) and powdered KOH (0.48 g, 7.3 mmol, 85% purity). The mixture was stirred for 2 h at 50–60 °C, poured into water, and extracted with diethyl ether. The ether layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving 1.40 g of the nitrile.

4-(2-Ethylbutyl)phenoxybutyraldehyde. 4-(2-Ethylbutyl)-phenoxybutyronitrile (1.2 g, 4.7 mmol) was dissolved in sodium-dried toluene (10 mL) under an N_2 atmosphere. Freshly prepared diisobutylaluminum hydride in toluene (4.4 mL, 1.5 M) was added dropwise, and the mixture was stirred for 2 h. The solution was then poured into 50 mL of 1 N H_2SO_4, and the mixture was stirred for 1 h. The toluene layer was removed, and the aqueous phase was extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, and freed of solvent under reduced pressure, giving 1.27 g of 4-(2-ethylbutyl)phenoxybutyraldehyde.

4-(2-Ethylbutyl)phenoxybutyraldoxime *O*-Methyl Ether (4a). An aqueous solution (5 mL) of *O*-methylhydroxylamine hydrochloride (0.47 g, 5.6 mmol) and 6 N HCl (0.2 mL) was added to 4-(2-ethylbutyl)phenoxybutyraldehyde (1.27 g, 5.1 mmol) in ethanol (30 mL). The mixture was stirred for 2 h at 50–60 °C, diluted with water, and extracted with *n*-hexane. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 10% ethyl acetate in *n*-hexane, giving 0.52 g (34%) of the oxime *O*-ether **4a**: ^{1}H NMR ($CDCl_3$) δ 7.36 (t, 1 H, J = 5 Hz, C*H*N), 6.88 (m, 4 H, Ar *H*), 3.93 (t, 2 H, J = 6 Hz, Ar OCH_2), 3.80 (d, 3 H, J = 3 Hz, OCH_3), 2.47 (d, 2 H, J = 5 Hz, Ar CH_2), 2.07 (m, 4 H, Ar $OCH_2CH_2CH_2$), 1.60 [m, 5 H, $CH(CH_2)_2$], 0.85 (t, 6 H, J = 5 Hz, CH_3).

Compound **4d** was prepared from 4-(1-ethylpropoxy)phenol according to an analogous method.

4-Bromobutyl Ethyl Ether. To a sodium ethylate solution (~10% in ethanol) (20 mL) was added 1,4-dibromobutane (10.0 g, 46 mmol), and the mixture was stirred for 48 h at room temperature, poured into water, and extracted with *n*-hexane. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was put on a silica gel column that was eluted with 5% ethyl acetate in *n*-hexane to give 3.30 g (39%) of the bromide.

4-[4-(2-Ethylbutyl)phenoxy]butyl Ethyl Ether (8a). To a Me_2SO solution (5 mL) of 4-(2-ethylbutyl)phenol (0.4 g, 2.2 mmol) and powdered KOH (0.19 g, 2.9 mmol, 85% purity) was added 4-bromobutyl ethyl ether (0.49 g, 2.7 mmol). The mixture was stirred for 2 h, poured into water, and extracted with *n*-hexane. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 10% ethyl acetate in *n*-hexane, giving 0.53 g (85%) of the ether **8a**: ^{1}H NMR ($CDCl_3$) δ 6.88 (m, 4 H, Ar H), 3.91 (t, 2 H, J = 6 Hz, Ar OCH_2), 3.47 (q, 2 H, J = 6 Hz, OCH_2CH_3), 3.45 (t, 2 H, J = 6 Hz, CH_2CH_2O), 2.43 (d, 2 H, J = 6 Hz, Ar CH_2), 1.78 (m, 4 H, $OCH_2CH_2CH_2CH_2O$), 1.25 [m, 5 H, $CH(CH_2)_2$], 1.16 (t, 3 H, J = 6 Hz, CH_3), 0.85 (t, 6 H, J = 6 Hz, $2CH_3$).

By an analogous method, compounds **6a–d**, **7a–d**, **8b–d**, and **10a,b** were prepared from the appropriate phenols and haloalkyl alkyl ethers.

4-(2-Ethylbutyl)phenoxyethyl Bromide. A mixture of 4-(2-ethylbutyl)phenol (0.5 g, 2.8 mmol), 1,2-dibromoethane (0.58 g, 3.1 mmol), and water (5 mL) was heated to boiling. To the boiling solution was added slowly a solution of NaOH (0.22 g, 5.6 mmol) in water (2 mL), and the mixture was refluxed for 1 h and then cooled and extracted with diethyl ether. The diethyl ether layer was washed with 3 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure to give 0.40 g (50%) of the oily bromide.

Isobutyraldoxime *O*-2-[4-(2-Ethylbutyl)phenoxy]ethyl Ether (12a). To a dimethylformamide (DMF) solution (5 mL) of NaH (0.14 g, 3.1 mmol, 53% purity) was added a DMF solution (1 mL) of isobutyraldoxime (0.22 g, 2.5 mmol) that had been synthesized from isobutyraldehyde and hydroxylamine. After bubbling stopped, 4-(2-ethylbutyl)phenoxyethyl bromide (0.80 g, 2.8 mmol) was added, and the mixture was stirred for 2 h at 100–120 °C, poured into water, and extracted with *n*-hexane. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was put on a silica gel column that was eluted with 5% ethyl acetate in *n*-hexane, yielding 0.27 g (37%) of the oxime ether **12a**: ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 1 H, J = 6 Hz, NC*H*), 6.87 (m, 4 H, Ar *H*), 4.23 (m, 4 H, OCH_2CH_2O), 2.62 (d, 2 H, J = 6 Hz, Ar CH_2), 2.30 [m, 1 H, $CH(CH_3)_2$], 1.23 [m, 5 H, $CH(CH_2)_2$], 1.07 [d, 6 H, J = 7 Hz, $CH(CH_3)_2$], 0.85 (t, 6 H, J = 6 Hz, $2CH_3$).

By an analogous method, compounds **11a,b** and **13a** were prepared from the appropriate phenols and oximes.

***N*-[4-(2-Ethylbutyl)phenoxypropyl]-*O*-ethylhydroxylamine (15a).** A methanol solution of 4-(2-ethylbutyl)phenoxypropionaldoxime *O*-ethyl ether (**3a**) (0.40 g, 1.4 mmol) was made acidic with HCl in methanol. To the solution was added $NaBH_3CN$ (0.14 g, 2.2 mmol), and then the mixture was stirred for 1 h, with a methanol solution of HCl being added dropwise to keep it acidic. The mixture was diluted with water, neutralized with $NaHCO_3$, and extracted with diethyl ether. The organic 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% ethyl acetate in *n*-hexane to give 0.37 g (92%) of the hydroxylamine **15a**: ^{1}H NMR ($CDCl_3$) δ 6.90 (m, 4 H, Ar *H*), 5.42 (br s, 1 H, N*H*), 4.00 (t, 2 H, J = 6 Hz, Ar OCH_2), 3.38 (q, 2 H, J = 7 Hz, $NHOCH_2$), 3.08 (t, 2 H, J = 7 Hz, CH_2NH), 2.45 (d, 2 H, J = 6 Hz, Ar CH_2), 1.97 (m, 2

H, Ar OCH_2CH_2), 1.25 [m, 5 H, $CH(CH_2)_2$], 1.17 (t, 3 H, J = 7 Hz, OCH_2CH_3), 0.87 (t, 6 H, J = 6 Hz, $2CH_3$).

Hydroxylamines **14a,c**, **15c**, and **16a–18a** were prepared according to a method analogous to the preparation of **15a**.

Ethyl 4-(2-Ethylbutyl)phenoxybutyrate (21a). A Me_2SO solution (5 mL) of 4-(2-ethylbutyl)phenol (0.5 g, 2.8 mmol), powdered KOH (0.24 g, 3.6 mmol, 85% purity), and ethyl 4-bromobutyrate (0.60 g, 3.1 mmol) was stirred for 3 h at room temperature. The mixture was poured into water and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and freed of solvent under reduced pressure, and the residue was purified by silica gel column chromatography with 10% ethyl acetate in *n*-hexane, yielding 0.73 g (89%) of the ester **21a**: ^1H NMR ($CDCl_3$) δ 6.85 (m, 4 H, Ar *H*), 4.10 (q, 2 H, J = 7 Hz, $COOCH_2$), 4.03 (t, 2 H, J = 6 Hz, Ar OCH_2), 2.47 (d, 2 H, J = 6 Hz, Ar CH_2), 2.10 (m, 4 H), 1.80 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.25 [m, 5 H, $CH(CH_2)_2$], 0.85 (t, 6 H, J = 6 Hz, $2CH_3$).

By an analogous method, compounds **19a**, **21b**, **22a**, **23a**, **24a,b**, **56**, and **58** were prepared from the appropriate haloesters.

3-[4-(2-Ethylbutyl)phenoxy]propionitrile. A toluene solution (50 mL) of 4-(2-ethylbutyl)phenol (2.0 g, 11 mmol), acrylonitrile (3.0 g, 57 mmol), and NaH (0.22 g, 0.5 mmol, 60%) was refluxed for 24 h; the mixture was washed with water, 1 N NaOH, and water, dried over $MgSO_4$, and concentrated under reduced pressure. The oily product was put on a silica gel column that was eluted with toluene, yielding 1.84 g (71%) of the nitrile.

3-[4-(2-Ethylbutyl)phenoxy]propionic Acid. An aqueous solution (7 mL) of concentrated H_2SO_4 (7 mL) and 3-[4-(2-ethylbutyl)phenoxy]propionitrile (0.8 g, 3.7 mmol) was refluxed for 3 h. After being cooled, the mixture was poured into water and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give 0.84 g (91%) of the acid.

Propyl 3-[4-(2-Ethylbutyl)phenoxy]propionate (20a). The propanol solution (15 mL) of 3-[4-(2-ethylbutyl)phenoxy]propionic acid (0.84 g, 3.4 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate was refluxed for 3 h. After being cooled, the mixture was poured into water and extracted with diethyl ether, and the extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 10% ethyl acetate in hexane to give 0.84 g (86%) of the ester **20a**: ^1H NMR ($CDCl_3$) δ 6.87 (m, 4 H, Ar *H*), 4.18 (t, 2 H, J = 6.5 Hz, $COOCH_2$), 4.05 (t, 2 H, J = 6.5 Hz, Ar OCH_2), 2.73 (t, 2 H, J = 6.5 Hz, CH_2CO), 2.43 (d, 2 H, J = 6 Hz, Ar CH_2), 1.58 (m, 2 H, $OCH_2CH_2CH_3$), 1.25 [m, 5 H, $CH(CH_2)_2$], 0.93 (t, 3 H, J = 6.5 Hz, CH_3), 0.87 (t, 6 H, J = 6 Hz, $2CH_3$).

Compound **57** was prepared by analogy with the preparation of compound **20**.

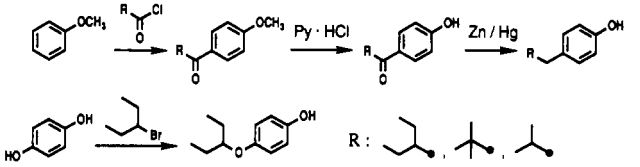
Ethyl (*E,Z*)-4-Bromo-3-methyl-2-butenoate. A CCl_4 solution of 3-methyl-2-butenoate (5.0 g, 39 mmol), *N*-bromosuccinimide (7.0 g, 39 mmol), and benzoyl peroxide (0.32 g, 13 mmol) was refluxed for 3 h. After the succinimide produced was removed by filtration, the CCl_4 solution was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving 11.2 g of the *E,Z* bromide.

Ethyl (*E*)- and (*Z*)-4-[4-(2-Ethylbutyl)phenoxy]-3-methyl-2-butenoate (26a and 27a). To a Me_2SO solution (5 mL) of 4-(2-ethylbutyl)phenol (0.40 g, 2.2 mmol) and powdered KOH (0.22 g, 3.3 mmol, 85% purity) was added ethyl 4-bromo-3-methyl-2-butenoate (0.93 g, 4.5 mmol). The mixture was stirred for 12 h, poured into water, and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and freed of solvent under reduced pressure. The residue was purified by silica gel column chromatography with 10% ethyl acetate in *n*-hexane, yielding 0.19 g (26%) of *E* isomer **26a** and 0.13 g (18%) of *Z* isomer **27a**: ^1H NMR ($CDCl_3$) δ (compound **26a**) 6.78 (m, 4 H, Ar *H*), 6.00 (m, 1 H, $CCHCO$), 4.43 (s, 2 H, Ar OCH_2), 4.13 (q, 2 H, J = 7 Hz, $COOCH_2$), 2.43 (d, 2 H, J = 6 Hz, Ar CH_2), 2.17 (s, 3 H, CCH_3), 1.27 (t, 3 H, J = 7 Hz, CH_3), 1.25 [m, 5 H, $CH(CH_2)_2$], 0.85 (t, 6 H, J = 6 Hz, $2CH_3$); (compound **27a**) 5.73 (m, 1 H, $CCHCO$), 5.13 (s, 2 H, Ar OCH_2), 2.00 (s, 3 H, CCH_3).

Compounds **25a**, **28a**, and **29a** were prepared from isopropyl ester by an analogous method.

4-(2-Ethylbutyl)phenoxypropyl Propionate (31a). To a pyridine solution (5 mL) of 4-(2-ethylbutyl)phenoxypropanol

Scheme I



(0.70 g, 3.0 mmol) was added propionyl chloride (0.32 g, 3.5 mmol). The mixture was stirred for 1 h, poured into water, and extracted with *n*-hexane. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 10% ethyl acetate in hexane, giving 0.50 g (59%) of the ester **31a**: ^1H NMR ($CDCl_3$) δ 6.87 (m, 4 H, Ar *H*), 4.23 (t, 2 H, J = 6 Hz, CH_2OCO), 3.97 (t, 2 H, J = 6 Hz, Ar OCH_2), 2.42 (d, 2 H, J = 6 Hz, Ar CH_2), 2.23 (m, 2 H, Ar OCH_2CH_2), 2.12 (q, 2 H, J = 6 Hz, $COCH_2$), 1.25 [m, 5 H, $CH(CH_2)_2$], 1.12 (t, 3 H, J = 6 Hz, CH_3), 0.87 (t, 6 H, J = 6 Hz, $2CH_3$).

By an analogous method, compounds **30a**, **32a–35a**, and **59–61** were prepared from the appropriate acid chlorides.

***N*-Ethyl-4-[4-(2-ethylbutyl)phenoxy]butyramide (38a).** An ethanol solution (20 mL) of the ester **21a** (0.73 g, 2.5 mmol) and KOH (0.20 g, 3.0 mmol, 85% purity) was refluxed for 2 h. After being cooled, the mixture was acidified with 6 N HCl and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, yielding 0.64 g (97%) of the acid, which was mixed with $SOCl_2$ (1 mL) and stirred for 3 h at room temperature. Excess $SOCl_2$ was removed from the mixture under reduced pressure, giving 4-[4-(2-ethylbutyl)phenoxy]butyryl chloride.

The chloride was added to a diethyl ether solution (10 mL) of ethylamine (about 2.6 g), and the mixture was stirred for 3 h and washed with water, 1 N HCl, and water. The organic layer was separated, dried over $MgSO_4$, and freed of solvent under reduced pressure. The residue was purified by silica gel column chromatography with 50% ethyl acetate in benzene, yielding 0.56 g (79%) of the amide **38a**: ^1H NMR ($CDCl_3$) δ 6.87 (m, 4 H, Ar *H*), 5.63 (br s, 1 H, N*H*), 3.93 (t, 2 H, J = 6 Hz, Ar OCH_2), 3.27 (m, 2 H, $NHCH_2$), 2.27 (t, 2 H, J = 6 Hz, CH_2CO), 1.23 [m, 5 H, $CH(CH_2)_2$], 1.08 (t, 3 H, J = 7 Hz, CH_3), 0.85 (t, 6 H, J = 6 Hz, $2CH_3$).

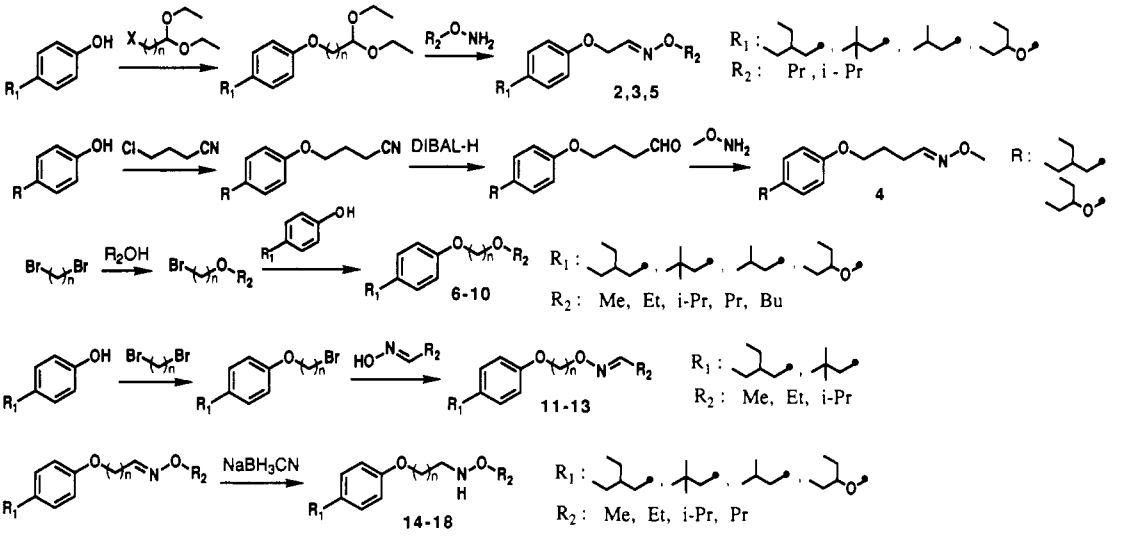
Compounds **36a**, **37a**, **39a**, and **40a** were prepared by a method analogous to that for the preparation of **38a**.

2-[4-(2-Ethylbutyl)phenoxy]ethyl *N*-Ethylcarbamate (41a). To a diethyl ether solution (5 mL) of 4-(2-ethylbutyl)-phenoxyethanol (0.35 g, 1.6 mmol) and triethylamine (0.1 mL) was added ethyl isocyanate (0.12 g, 1.7 mmol). The mixture was stirred for 2 h, poured into water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was put on a silica gel column that was eluted with 30% ethyl acetate in *n*-hexane, giving 0.44 g (95%) of the carbamate **41a**: ^1H NMR ($CDCl_3$) δ 6.90 (m, 4 H, Ar *H*), 4.87 (br s, 1 H, N*H*), 4.23 (m, 4 H, OCH_2CH_2O), 3.20 (m, 2 H, $NHCH_2$), 2.45 (d, 2 H, J = 6 Hz, Ar CH_2), 1.25 [m, 5 H, $CH(CH_2)_2$], 1.10 (t, 3 H, J = 7 Hz, CH_3), 0.87 (t, 6 H, J = 6 Hz, $2CH_3$).

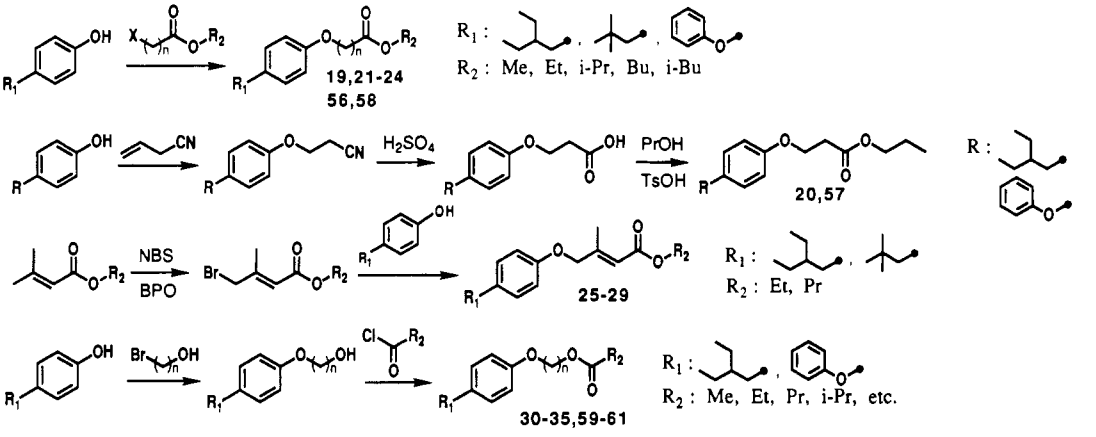
By an analogous method, compounds **41b**, **42a,b**, **43a**, **46a**, and **48a** were prepared from the appropriate isocyanates.

Ethyl *N*-2-[4-(2-Ethylbutyl)phenoxy]ethylcarbamate (49a). An ethanol solution (1 mL) of 2-chloroethyl isocyanate (0.36 g, 3.4 mmol) and triethylamine (0.1 mL) was stirred for 1 h, and to the solution were added 5 mL of DMSO, 4-(2-ethylbutyl)-phenol (0.5 g, 2.8 mmol), and powdered KOH (0.24 g, 3.6 mmol, 85% purity). The mixture was stirred for 12 h at 50–60 °C, poured into water, and extracted with diethyl ether. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with 30% ethyl acetate in *n*-hexane, giving 0.50 g (61%) of the carbamate **49a**: ^1H NMR ($CDCl_3$) δ 6.87 (m, 4 H, Ar *H*), 5.16 (br s, 1 H, N*H*), 4.10 (q, 2 H, J = 7 Hz, $COOCH_2$), 3.97 (t, 2 H, J = 4 Hz, Ar OCH_2), 3.57 (t, 2 H, J = 5.5 Hz, CH_2NH), 2.45 (d, 2 H, J = 6 Hz, Ar CH_2), 1.25 [m, 5 H, $CH(CH_2)_2$], 1.23 (t, 3 H, J = 7 Hz, OCH_2CH_3), 0.87 (t, 6 H, J = 6 Hz, $2CH_3$).

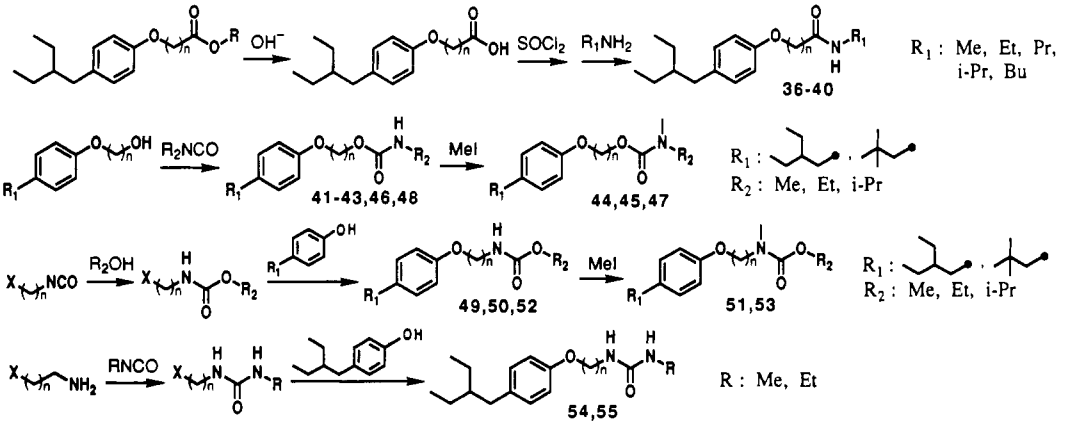
Scheme II



Scheme III



Scheme IV



Compounds **49b**, **50a,b** and **52a** were prepared according to a method analogous to that for the preparation of **49a**.

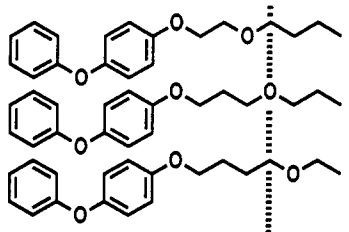
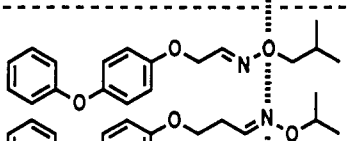
Methyl *N*-3-[4-(2-Ethylbutyl)phenoxy]propyl-*N*-methylcarbamate (53a). To a benzene solution (5 mL) of NaH (0.17 g, 3.8 mmol, 53% purity) was slowly added methyl *N*-3-[4-(2-ethylbutyl)phenoxy]propylcarbamate (**52a**) (0.64 g, 2.2 mmol). After bubbling stopped, CH_3I (0.48 g, 3.4 mmol) was added and the mixture was stirred for 12 h at 50–60 °C and poured into water. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 20% ethyl acetate in *n*-hexane, giving 0.27 g (40%) of the carbamate: ^1H NMR ($CDCl_3$) δ 6.87 (m, 4 H, Ar *H*), 3.92 (t, 2 H, J = 6 Hz, Ar OCH_2), 3.62 (s, 3 H, OCH_3), 3.43 (t, 2 H, J = 6 Hz, CH_2N), 2.88 (s, 3 H, NCH_3), 2.47 (d, 2 H, J = 6 Hz, Ar CH_2), 1.97 (m, 2 H, Ar OCH_2CH_2), 1.23 [m, 5 H, $CH(CH_2)_2$], 0.87 (t, 6 H, J = 6 Hz, $2CH_3$).

By an analogous method, compounds **44a**, **45a**, **47a**, and **51a** were prepared from the appropriate carbamates.

***N*-[3-[4-(2-Ethylbutyl)phenoxy]propyl]-*N'*-methylurea (55a).** To a diethyl ether solution (10 mL) of methylamine (about 1 g) was added 3-chloropropyl isocyanate (0.8 g, 6.7 mmol). The mixture was stirred for 1 h and concentrated under reduced pressure, yielding 0.87 g (86%) of crude *N*-(3-chloropropyl)-*N'*-methylurea.

To a Me_2SO solution (5 mL) of 4-(2-ethylbutyl)phenol (0.5 g, 2.8 mmol) and powdered KOH (0.24 g, 3.6 mmol, 85% purity) was added *N*-(3-chloropropyl)-*N'*-methylurea (0.51 g, 4.8 mmol).

Table I. Structure and Activity against *C. pipiens* of 4-Phenoxyphenoxyalkyl Alkyl Ethers and Related Oximes Showing the Position of the Functions vs Activity Relationship[a]

Structure	pI_{50}[b]
	8.08
	9.47
	7.93
	8.72
	9.76

[a] The broken line at the δ position from the phenoxy oxygen atom shows the position-specific interaction site with the receptor. [b] Logarithm of the reciprocal of the molar concentration at which 50% inhibition of metamorphosis is observed. The data were taken from the literature (Niwa et al., 1990).

The mixture was stirred for 4 h at 50–60 °C, poured into water, and treated with diethyl ether. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 10% ethyl acetate in *n*-hexane, yielding 0.79 g (96%) of the urea **55a**: ^1H NMR ($CDCl_3$) δ 6.87 (m, 4 H, Ar *H*), 5.47 (br s, 2 H, 2N*H*), 3.90 (t, 2 H, *J* = 6 Hz, Ar OCH_2), 3.30 (m, 2 H, CH_2NH), 2.67 (s, 3 H, NHCH_3), 2.43 (d, 2 H, *J* = 6 Hz, Ar CH_2), 1.87 (m, 2 H, CH_2), 1.20 [m, 5 H, $CH(CH_2)_2$], 0.85 (t, 6 H, *J* = 6 Hz, 2CH_3).

By an analogous method, compound **54a** was prepared.

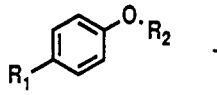
In the synthesis of oximes, both *E* and *Z* isomers were produced; the ratio was estimated to be about 1:1 from ^1H NMR examination (Nakayama et al., 1985). The oximes could not be separated by conventional chromatography, and thus a mixture of the two isomers was bioassayed.

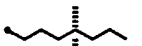
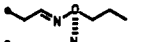
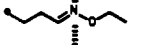
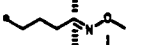
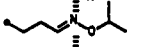
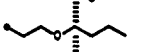
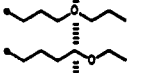
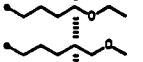
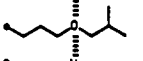
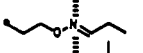
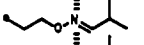
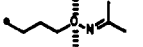
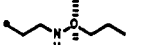
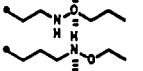
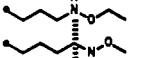
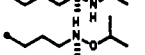
The reaction pathways are summarized in Schemes I–IV. All of the final products were identified by elemental analyses for C, H, and N within ±0.3% error. This information is available as supplementary material.

Bioassay Procedure. Fourth larval instars of *Culex pipiens pallens* 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 Sumitomo Chemicals 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 a test compound then was added to the tumblers, after which the diet powder was added. The tumblers were covered with transparent plastic cups to prevent adults from flying away. After 7 days at 28 °C, the results were scored as the percentage adults that had not emerged, including those that could escape only partly from the pupal cuticles. The experimental results in the bioassays were checked mostly by replication when a high rating (usually at least 50% inhibition of metamorphosis) was recorded, but experiments usually were not repeated at concentrations that had low activity. When an abnormal rating was found, repetitions were made at that and neighboring concentrations. When more than one abnormal rating was obtained, the experiment was repeated for the entire concentration range. All of the data excluding the abnormal values were averaged. The nonemergence percentage of the control (no chemicals added except 10 μL of ethanol) was less than 10% through the experiments.

The activity was expressed in terms of pI_{50} (M), the logarithm of the reciprocal of the concentration at which 50% of metamorphosis is inhibited. The data are summarized in Tables II and III together with those for methoprene and fenoxycarb as references. Methoprene was provided by Earth Chemical Co., Ltd.

Table II. Structure and Activity against *C. pipiens* of (4-Substituted)phenyl *n*-Heptyl Ether and Related (4-Substituted)phenoxy Compounds with Ether, Oxime, and Hydroxylamine Functions[a]



No.	R_2	pI_{50} (M) R_1: a	b	c	d
1		5.18			
2		8.40	6.54	5.39	7.83
3		9.53	8.57	8.29	8.19
4		6.66			6.23
5		10.76	10.03	10.85	9.30
6		6.78	6.36	6.44	5.49
7		8.17	8.01	7.86	6.80
8		6.68	6.66	6.48	5.98
9		5.71	5.29	5.35	5.04
10		8.81	9.43		
11		9.88	9.50		
12		9.71			
13		8.65			
14		7.33		6.57	
15		8.43		7.81	
16		6.30			
17		8.97			
18		8.66			

[a] The broken line made on the δ position from the phenoxy oxygen atom shows the position-specific interaction site with the receptor. pI_{50} expresses the logarithm of the reciprocal of the molar concentration at which 50% inhibition of metamorphosis is observed.

Calculations. The stable conformation of compounds was studied by molecular orbital methods. The computation was done by use of AMPAC (QCPE No. 523) with AM1 parametrization (Dewar and Stewart, 1985; Dewar, 1986). The starting coordinates were obtained from ANCHOR (Kureha Chemical Industry Co., Ltd., and Fujitsu Ltd., Tokyo, Japan), a program system for molecular modeling. The electrostatic potentials were calculated for the optimum geometry from the point charges on the atomic centers and plotted as shown in Figure 2.

Hydrolysis and Ester-Exchange Reactions. The hydrolysis was carried out at 25 °C and at boiling in AcCN/H_2O (1:1), which was adjusted to pH 1.1, 3.3, and 4.6 with 2 N HCl and to pH 11.5 with 1 N NaOH. The concentration of the test compounds was 10 mg/mL. Ester exchange was done with 5 mL of 2-propanol in the presence of 20 mg of *p*-toluenesulfonic acid monohydrate, the concentration of the compounds being 0.80 g/5 mL. A 2-μL portion of medium was injected into the HPLC column (Wakosil 5C18, 4.6 × 250 mm), which was eluted with a gradient of AcCN in water from 0% to 10% at the flow rate of 0.5 mL/min. Monitoring was at 254 nm, and the concentration was calculated from the peak area.

Table III. Structure and Activity against *C. pipiens* of (4-Substituted)phenoxy Compounds with Ester, Amide, Carbamate, and Urea Functions[a]

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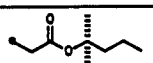
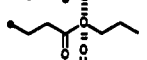
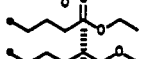
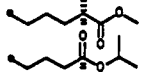
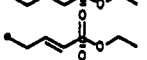
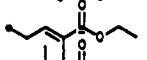
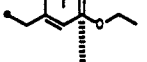
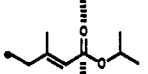
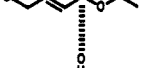
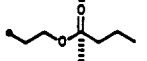
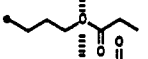
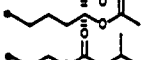
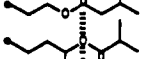
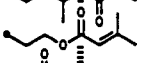
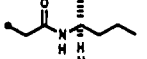
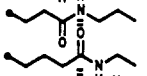
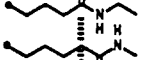
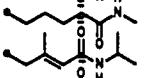
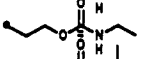
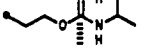
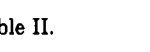
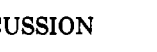
19		—	
20		—	
21		—	—
22		—	
23			—
24		5.74	5.82
25		5.84	
26		E 8.36	
27		Z 6.62	
28		E 9.08	
29		Z 7.79	
30		—	
31		—	
32		—	
33		—	
34		5.32	
35		6.82	
36		5.09	
37		4.81	
38		5.87	
39		5.15	
40		6.99	
41		7.57	6.87
42		8.62	8.23

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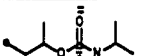
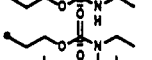
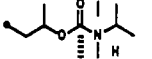
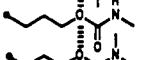
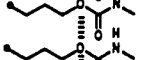
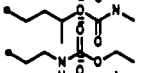
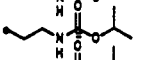
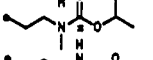
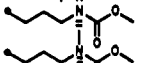
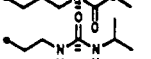
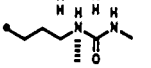
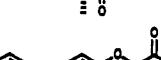
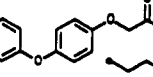
43		7.95	
44		8.59	
45		8.25	
46		6.50	
47		7.77	
48		7.11	
49		7.54	7.70
50		8.12	7.78
51		7.86	
52		6.31	
53		6.79	
54		6.97	
55		4.83	
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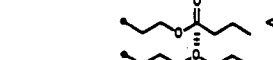
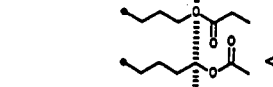
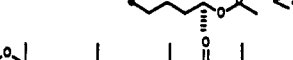
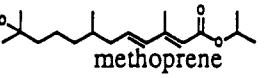
57		4.91	
58		<4.5	
59		<4.5	
60		5.02	
61		<4.5	
	methoprene	9.50	
	fenoxycarb	8.82	

[a] See footnote *a* of Table II.

RESULTS AND DISCUSSION

JH Activity and Structure. The substituents attached to the 4-position of the phenoxy moiety were usually 2-ethylbutyl, neopentyl, isobutyl, or 1-ethylpropoxy (Tables II and III), which are the groups that help to confer high JH mimetic activity in the previously reported (4-substituted-phenoxy)alkanaldoxime *O*-ether series of compounds (Hayashi et al., 1989). The overall length of the molecules in their extended conformation was kept in 20–21 Å, the value calculated to be most favorable for high potency (Nakayama et al., 1985; Niwa et al., 1988, 1989, 1990; Hayashi et al., 1989). Within this framework, the position of a functional group in the molecule was varied so as to examine its positional and electrostatic effects on activity.

Compound **1a**, 4-(2-ethylbutyl)phenyl *n*-heptyl ether with no functional group in the alkyl moiety, was prepared as a reference. The oxime compounds **2a–c**, **3a–d**, and **4a,d** are congeners of the previous (4-substituted-phenoxy)alkanaldoxime *O*-ethers, and **2d** and **5a–d** are the members with the highest activity of their class (Hayashi et al., 1989). Compounds **6–10** are entities with the simplest function, ether, and **11–13** are compounds in which the oxime function is incorporated in a way opposite to **2–5**.

The positional effect on the activity of these oxime and ether functions has already been examined in 4-phenoxyphenoxy congeners of the present series of compounds (Niwa et al., 1990). In the single atomic ethers, the potency is highest when the oxygen atom is at distance δ from the central phenoxy oxygen atom in the molecule of optimum length. It is, in other words, about 4.6 Å from one end of the molecule with the optimum length. In the multiatomic oximes, the potency is highest when nitrogen, not oxygen, is at δ. This situation is shown in Table I for the (4-phenoxy)phenoxyalkyl alkyl ethers and (4-phenoxy)phenoxyalkanaldoxime *O*-ethers; the vertical broken line indicates the pertinent site.

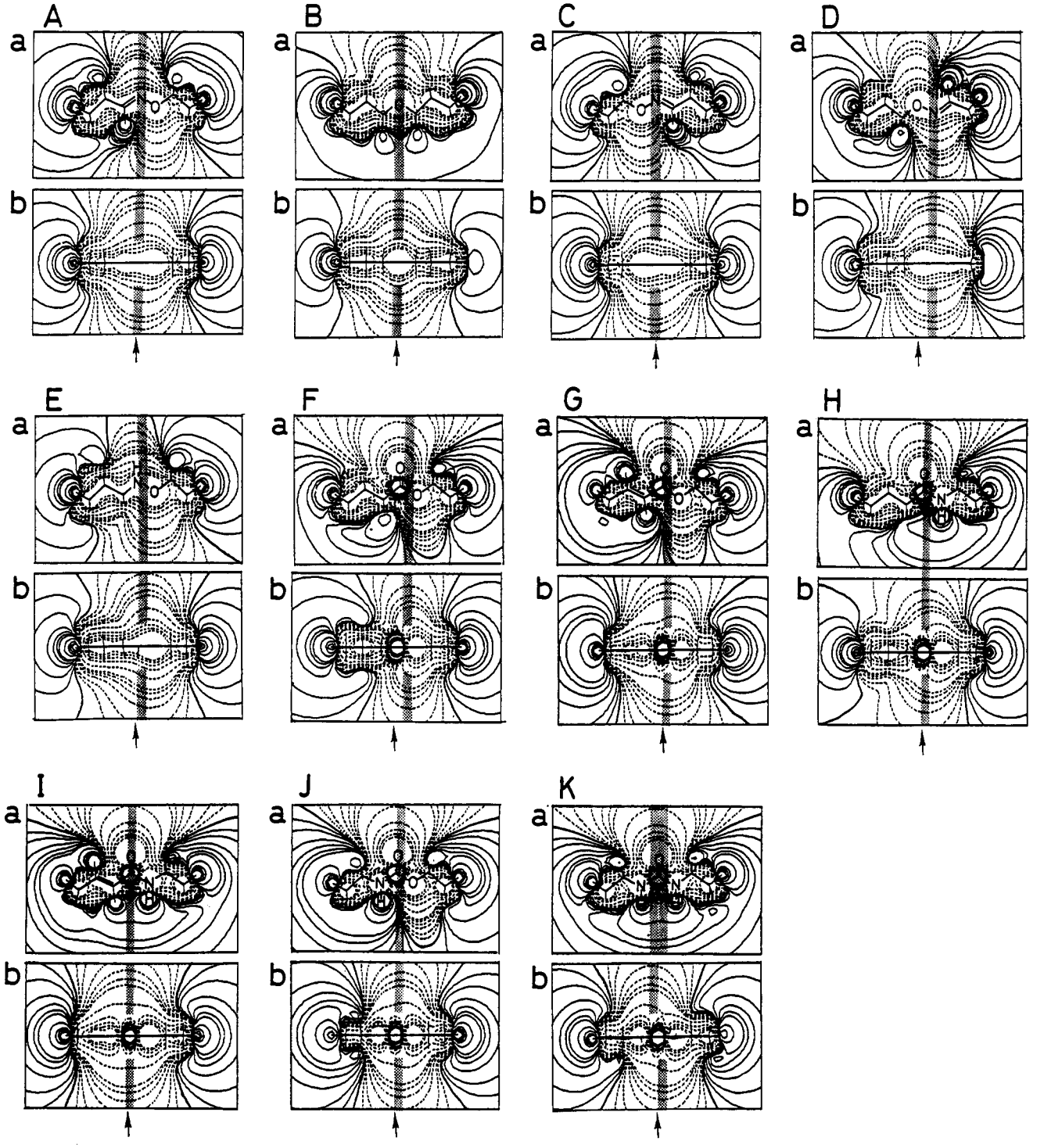


Figure 2. Contours of electrostatic potentials: (—) positive contours; (- - -) negative contours; (—) zero contour. The a series shows the map in the zigzag, extended molecular plane, and the b series shows the map in a plane that bisects the molecule vertically. The horizontal line in the middle of the b series shows the molecular skeleton on which the component atoms are lined up. The ends of bars of the structures indicate hydrogen atoms. The shadowing in the b series shows the site of the peak of the electrostatic potentials found at about the van der Waals surface of the molecule in the vertical plane. Shadowing is also shown on the a series as an extension of that in the b series, and it indicates the site of the peak located on the zigzag molecule. The arrow under the b series shows the δ site from the phenoxy oxygen atom of the JH molecules or the site 4.6 Å distant from the other end of the molecule.

In the compounds listed in Table II, the same was observed. δ-Ethers **7a–d** were more potent than corresponding γ- and ϵ-ethers **6a–d** and **8a–d**, δ-nitrogenous oximes **3a–d** were more potent than γ-oximes **2a–d** and ϵ-oximes **4a–d**, and δ-nitrogenous **12a** was more potent than ϵ-oxime **13a**. In hydroxylamines, the potency was higher when a nitrogen was at the δ site (compounds **15a,c**) than when it was at γ (compounds **14a,c**) or ϵ (compound **16a**), although ϵ-**16a** was less potent than γ-**14a**. The examination was extended to functions other than these—the esters, amides, carbamates, and ureas seen in compounds **19–55** in Table III. Such functions are often found in JH mimetic compounds hitherto known (Henrick, 1982). The broken line drawn on the structures in Tables II and III shows the site of interest.

The potency of simple esters (**19–23** and **30–33**), except for the doubly branched **34a**, was undetectably poor, so that we could not observe the positional effects of the function. For that reason, we prepared the 4-phenoxyphenoxy congeners **56–61**. Of these, only the potency of

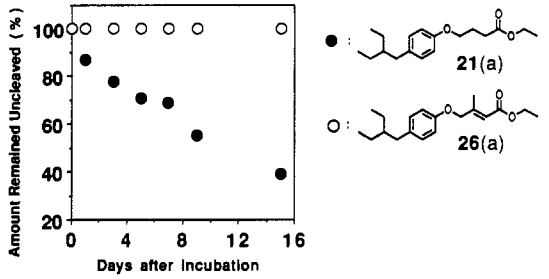


Figure 3. Rate of hydrolysis of the simple ester, ethyl 4-[4-(2-ethylbutyl)phenoxy]butyrate (**21a**), and the α,β-unsaturated ester, ethyl 4-[4-(2-ethylbutyl)phenoxy]-3-methyl-2-butenoate (**26a**), at pH 1.1 and 25 °C.

δ-oxygenous **57**, **58**, and **60** was high enough to be detected, which seems to suggest that the other positional isomers were still less favorable for activity.

The potency of the α,β-unsaturated esters **24a–29a** was higher, especially that of (*E*)-**28a** with two methyl branches, with activity as high as that of methoprene and fenoxycarb [ethyl *N*-(4-phenoxyphenoxy)ethylcarbamate]. The *Z* isomer of this ester was dozens of times less potent, and its steric dimensions seemed to be unfavorable for fitting the receptor. Similarly, α,β-unsaturated **35a** was more potent than the saturated congener **33a**. In these unsaturated esters, the δ site was occupied by the carbonyl group rather than the alcoholic oxygen atom.

The amides **36a–39a**, in which the ester oxygen of compounds **19a–22a**, without activity, were replaced by NH, had detectable activity. The introduction of α,β-unsaturation and a methyl branch into **38a** gave **40a**, the amide congener of **26a**. The potency was higher, but not as high as expected from the results of the esters (compare the potency of the simple ester **21a** with that of unsaturated **26a**). Among the simple amide congeners **36a–39a**, **38a**, the carbonyl function of which is at the δ site, was most potent, and δ-nitrogenous **37a** was less potent. Carbamates **41a** and **46a** were considerably more potent than the corresponding amides **38a** and **39a**. Concerning the positional effect, the δ-carbonyl congener **41a** was more potent than δ-oxygenous **46a**, suggesting that the potency is higher when the carbonyl group is at the δ site than when it is not. Similar effects were observed for the compounds in which the carbamate function was incorporated in an opposite way, δ-carbonyl **49a** being more potent than δ-nitrogenous **52a**. The ureas **54a** and **55a** were less potent than the corresponding carbamates **50a** and **52b**, but the trend in which the δ-carbonyl compound **54a** was more favorable for activity than the δ-nitrogenous congener **55a** was the same.

Among the new series of compounds developed in this study, ether **10b**, oximes **11a,b** and **12a**, hydroxylamine **17a**, and α,β-unsaturated ester **28a** had potency as high as that of methoprene.

Electrostatic Potentials. The calculation of the electrostatic potentials was made for molecules from which the (4-substituted)phenoxy moiety was subtracted. We used the energy minimum conformation calculated as described under Experimental Procedures, and the skeletal seven atoms from the common phenoxy oxygen atom were caused to overlap as completely as possible those of the oxime compound (Figure 2A) by least-squares fitting. The potential contours of the zigzag plane are shown in the a series of Figure 2, and those of the plane that bisects the zigzag molecule at its geometrical center are in the b series.

Figure 2A for the oxime and Figure 2B for the ester are from our previous calculations (Hayashi et al., 1990b). Important here is that the contour lines are distributed symmetrically with a negative peak through the upper and lower sides of the molecule in the b series. The site of the peak was found on the contour at about the van der Waals surface of the molecule that could be assumed to be the frontier of the contact with the receptor. The shadowing in b indicates this site and is extended upward to the a series to show where the peak is on the zigzag molecule.

In the case of ethers (Figure 2B), the peak was at the oxygen site, and in the oximes (Figure 2A), it was at the nitrogen site, not at the oxygen site. Thus, the peak moves to the right or left depending on the position of the functional groups. In previous examinations of these oxime and ether functions and for aromatic phenyl, phenoxy, pyridyl, and pyridyloxy groups (Hayashi et al., 1990b), the potency was found to be highest in a congeneric functional series when the negative peak was about 4.6 Å distant from one end of the molecule, which is evidence that the electrostatic interaction with the receptor is then most favorable. Each panel of Figure 2 was drawn so that its center would correspond to the 4.6-Å site, that is, to the δ position.

Figure 2C corresponds to the reverse oximes **11** and **12**, and Figure 2D corresponds to **13**, the negative peak being at the nitrogen site. This explains why δ-nitrogenous **12a** was more potent than ϵ-**13a**. In hydroxylamines (Figure 2E), the negative peak seemed to be somewhere between the nitrogen and oxygen atoms, and this explains why **16a** was far less potent than **14a** and **15a**. The higher potency of **15a,c** than of **14a,c** may suggest that the peak may be somewhat nearer the nitrogen site.

The simple esters have their negative peak between the carbonyl carbon and ester oxygen atoms, probably somewhat nearer the oxygen atom (Figure 2F). This explains why among **56–58** δ-oxygenous 4-phenoxyphenoxy **57** was more potent than γ-**56** and ϵ-**58**, and the situation is thought to be similar in **59–61**. In the α,β-unsaturated esters in Figure 2G, the negative peak was closer to the carbonyl group. The situation was similar for the reverse type of esters **34a** and **35a** (data not shown). In the simple amides **36a–39a**, the negative peak was between the carbonyl and amino groups but closer to the carbonyl (Figure 2H). Probably, the negative peak of δ-carbonyl amide **38a** fits the 4.6-Å site of the receptor better than γ-**37a**, and thus the former has the higher activity. The α,β-unsaturated amide group had the negative peak at the carbonyl site (Figure 2I).

In the three atomic carbamates, the δ-carbonyl **41a** was more potent than the corresponding ϵ-carbonyl **46a**, and in the reverse type of carbamates, the potency of δ-carbonyl **49a** was higher than that of ϵ-carbonyl **52a**. This may reflect the peak of carbamates being at the position closer to the carbonyl function rather than to the oxygen atom (Figure 2J). These findings suggest that the role of the functions in interaction with the receptor is an electronic one, site-specific and directional, as has been suggested before (Hayashi et al., 1990b).

The δ-carbonylurea **54a** was far more potent than ϵ-**55a**. Unexpectedly, the urea structure in Figure 2K gave a negative peak at the left edge of the carbonyl function in the upper side of the zigzag molecule and in the lower side it gave the peak at the right edge. Yet the activity difference between **54a** and **55a** can be understood by the position of the negative potential; it locates close to the carbonyl group whichever side of the molecule interacts with the receptor.

Reactivity Considerations. The stereochemical as well as electrostatic considerations described above show

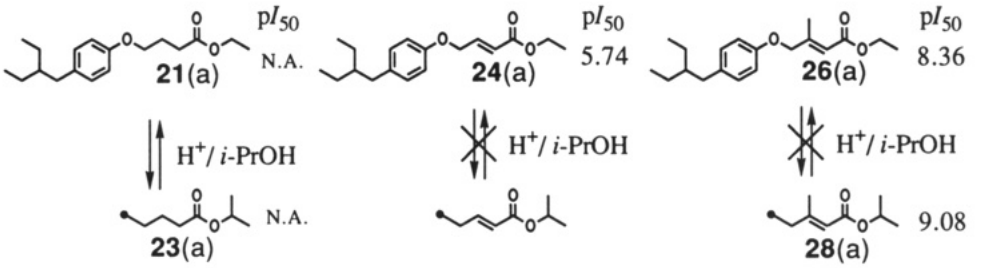


Figure 4. Ester-exchange profile of ester compounds in boiling 2-propanol in the presence of *p*-toluenesulfonic acid. The pI_{50} value is taken from Table III. N.A., not active.

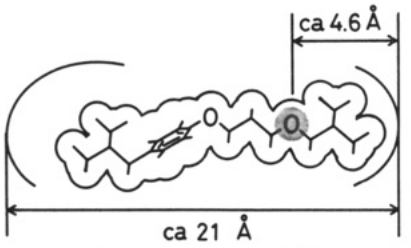


Figure 5. Accommodation of 4-neopentylphenoxy isobutoxypropyl ether (**10b**) in the JH mode of action map. The solid lines indicate the steric interaction site or the framework of the receptor. The shadowed circle indicates the position-specific site of electrostatic interaction with a heteroatom or a functional group of the JH molecule.

that the potency of the simple esters **19a–23a** was anomalously low compared with that of the α,β-unsaturated compounds **24a–26a** and **28a**. Thus, we sought reasons in other properties than these by examining the stability of the esters in acidic and alkaline solutions.

Figure 3 shows the hydrolytic rate of the simple ester **21a** and the α,β-unsaturated compound **26a** at pH 1.1 at 25 °C. About half of the **21a** was hydrolyzed in 8 days, the period for which insects were treated with a compounds in the assay, but **26a** was not hydrolyzed at all. At the higher pHs of 3.3 and 4.6 and even at an alkaline pH of 11.5, both compounds were hydrolyzed little during an incubation period of 16 days at 25 °C. Similarly, the ester-exchange reaction of saturated **21a** and unsaturated **24a** and **26a** was carried out in 2-propanol at 25 °C in the presence of *p*-toluenesulfonic acid, and both changed little. When boiled, however, half of **21a** changed to the corresponding isopropyl ester within 2 h, but surprisingly enough, the unsaturated esters **24a** and **26a** remained intact even after being boiled overnight (data not shown but see Figure 4). Thus, α,β-unsaturation makes esters very stable. The solution at pH 1.1 may not resemble the physiological conditions under which the compounds act in the body of insects; the high potency of the α,β-unsaturated esters is likely to be due to their resistance to chemical and enzymatic hydrolysis. Incidentally, methoprene, the α,β-unsaturated, highly potent JH mimic, behaved like **26a** in these reactions.

The amides seem to be less reactive than the ethers, and the amide compound **38a** was not, in fact, cleaved when incubated at pH 1.1 and 25 °C for 8 days. The carbamate **50a** and the carbamate JH mimic fenoxycarb also changed little (data not shown). This difference in reactivity seems to be at least one reason the simple amides **34–39** and carbamates **41–53** had more potency than the simple esters.

Conclusion and Prospects. A study of electrostatic features vs activity of aromatic functions like phenyl, phenoxy, and pyridyloxy (Hayashi et al., 1990b) was extended to nonaromatic groups like ester, amide, carbamate, and urea. The electrostatic contour maps had a common feature, a negative peak, when viewed in the section that bisects the zigzag plane of the molecules. The position of the peak explained the relationship between potency and the position of the functions in the molecules. As in the previous study, an important clue was that the potency was highest when the peak was about 4.6 Å distant from one end of the molecules of optimum size (about 21 Å) or from the receptor end that encompasses the part of the molecule containing the functions. The situation is shown in Figure 5, where the member with the highest effects, **10b**, of the single atomic ether compounds is accommodated in a JH receptor model that was previously suggested (Hayashi et al., 1990b).

The results provide a basis for the design of a potent JH active compound. A molecule should be built so that the negative potential peak of some function with a peak is located on the right at the 4.6-Å position within the framework of the optimum dimensions shown in Figure 5. This principle can now be applied to those compounds active against *C. pipiens*, since, for this insect, the most effective size of the molecule and the point of the electrostatic interaction have been studied in most detail. Application to other insect species might be possible if we could find a suitable size and site of electrostatic interaction by examining the activity of a set of compounds in which the structure and position of the function were systematically varied. The correspondence between the structure–activity relationships of a set of compounds has been examined for a variety of insects with reference to the structure–activity relationship for *C. pipiens* in the following paper (Hayashi et al., 1991).

Another point of interest to be examined in the future is why the potency is different in the most active members of different classes, although they satisfy the stereochemical and electrostatic conditions to about the same degree. Multiatomic or carbonyl series of compounds like esters (**19–23**), amides (**36–40**), carbamates (**41–53**), and ureas (**54, 55**) tend to be less potent than the single atomic or non-carbonyl ethers (**6–10**), oximes (**2–5** and **11–13**), and hydroxylamines (**14–18**). The cause may not be in the interaction with the receptor but in the processes by which the compounds reach the site of action. The multiatomic or carbonyl compounds could be more easily affected by a variety of biomolecules.

This line of investigation caused us to notice that the potency of simple esters was abnormally low compared with that of α,β-unsaturated esters, and this led us to examine the lability or stability of both against hydrolysis. The results showed that α,β-unsaturated compounds were unexpectedly resistant to ester hydrolysis in both acidic and alkaline solutions and suggested that this stability was at least partly responsible for their high potency. If this property is present and the steric and electrostatic conditions are met, the compound will probably be highly potent, like **28a**.

The α,β-unsaturated ester structure has been found in

naturally occurring JHs and also in highly potent members of the terpenoid type of JH mimetics like methoprene. It is likely that the structure is involved in resistance to nonbiological chemical hydrolysis as well as to enzymatic hydrolysis, although there is no biochemical evidence for this.

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Supplementary Material Available: Table of analytical data for (4-substituted)phenyl ethers (4 pages). Ordering information is given on any current masthead page.

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