Development of 4-Alkylphenyl Aralkyl Ethers and Related Compounds as Potent Insect Juvenile Hormone Mimetics and Structural Aspects of Their Activity

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We prepared as insect juvenile hormone mimetics 4-alkylphenyl phenylalkyl and phenoxyalkyl ethers and corresponding pyridine derivatives, in which the oxime moiety of the (4-alkylphenoxy)-alkanaldoxime *O*-ethers we have already developed is replaced by an aromatic function. The activity, examined against *Culex pipiens*, of the most potent member was comparable to that of the most active JH mimetics so far known. Their structure–activity profiles were compared with those of the previous, nonaromatic ethers, oximes, and related compounds to make the features characteristic to the aromatic function apparent.

We have been developing classes of insect juvenile hormone (JH) mimetic compounds; they are terpenoid undecen-2-one oxime *O*-ethers and undecen-2-yl carbamates (Nakayama et al., 1985), nonterpenoid (4-phenoxyphenoxy)alkanaldoxime *O*-ethers (Niwa et al., 1988), (4-phenoxyphenoxy)alkyl alkyl ethers (Niwa et al., 1989), *N*-(4-phenoxyphenoxy)-*O*-alkyl- and *O*-(4-phenoxyphenoxy)-*N*-alkylhydroxylamines (Niwa et al., 1990), 4-benzylphenoxy congeners of these, and (4-alkoxy- and 4-alkylphenoxy)alkanaldoxime *O*-ethers (Hayashi et al., 1989). Through these studies, common features found to be important for high JH-mimetic activity are overall molecular dimensions as well as localized ones, and the position of the nitrogenous or oxygenous function in the molecules. In this study, we prepared 4-alkylphenyl phenylalkyl and phenoxyalkyl ethers and their pyridine congeners. These are compounds in which the oxime moiety of the (4-alkylphenoxy)alkanaldoxime *O*-ethers we have already developed (Hayashi et al., 1989) is replaced by an aromatic function. Another aspect of the design is that they are entities in which the 4-phenoxyphenoxy moiety of JH-mimetic 4-phenoxyphenyl benzyl ethers (Karrer and Farooq, 1980) and (4-phenoxyphenoxy)alkyl pyridyl ethers (Ohsumi et al., 1985) is replaced by 4-alkylphenoxy. This was done on the basis of the previously discovered fact that the 4-alkylphenoxy structure is bioisosteric to the 4-phenoxyphenoxy moiety of active JH mimetics (Hayashi et al., 1989). Figure 1 shows their generic formulas.

The activity examined for *Culex pipiens* of the most potent member of the phenylalkyl and phenoxyalkyl series, 4-(2-ethylbutyl)phenyl 4-(isopropoxy)benzyl ethers, was a few times less potent than that of methoprene [isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate] (Hendrick et al., 1973), one representative of the highly active JH mimetics. In the corresponding pyridine series, 4-(2-ethylbutyl)phenyl 2-(2-pyridyloxy)ethyl ether had a potency higher than that of methoprene and comparable to that shown by our previous, nonterpenoid classes of compounds. Their structure–activity profiles were compared to those of the previous oximes and related compounds, highlighting the uniqueness that is attributable to the aromatic ring they have in place of the nonaromatic functions.

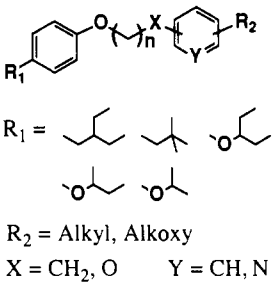

Figure 1. Generic formulas of the compounds studied.

EXPERIMENTAL PROCEDURES

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

4-Isobutylbenzyl Chloride. A mixture of isobutylbenzene (3.0 g), paraformaldehyde (1.5 g), concentrated hydrochloric acid (3 mL), glacial acetic acid (2.7 g), phosphoric acid (1.1 g), and a catalytic amount of $ZnCl_2$ was agitated at 100 °C for 24 h. After being cooled to room temperature, the mixture was dissolved in water and then extracted with *n*-hexane. The *n*-hexane layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by a silica gel column that was eluted with 2% ethyl acetate in *n*-hexane, to give 1.47 g (36%) of the 4-isobutylbenzyl chloride as an oil.

4-Propyl, 4-*sec*-butyl, 4-*tert*-butyl, and 4-neopentylbenzyl chloride were prepared from a substituted benzene by a method analogous for the preparation of 4-isobutylbenzyl chloride.

4-Propoxybenzyl Bromide. To a DMSO solution (5 mL) of 4-cresol (1.00 g, 9.3 mmol) were added propyl bromide (1.37 g, 11.1 mmol) and powdered KOH (0.92 g, 14.0 mmol, 85% purity). The mixture was stirred for 1 h at room temperature, diluted with water, and treated with *n*-hexane. The *n*-hexane layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, to yield 1.41 g (quantitative) of 4-propoxytoluene as an oil.

A mixture of crude 4-propoxytoluene (1.41 g), *N*-bromosuccinimide (NBS) (1.67 g, 9.3 mmol), benzoyl peroxide (BPO) (0.08 g, 0.03 mmol), and carbon tetrachloride (10 mL) was heated under reflux for 3 h. The mixture was filtered, and the filtrate 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 1.82 g (86%) of 4-propoxybenzyl bromide.

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By analogous methods 4-propoxybenzyl, 4-ethoxy, 4-isopropoxy, and 2-methoxybenzyl bromide were prepared.

Phenylbutyl Chloride. A mixture of carbon tetrachloride (5 mL), phenylbutyl alcohol (0.6 g, 4.0 mmol), and triphenylphosphine (1.36 g, 5.2 mmol) was refluxed for 1 h. The mixture was diluted with *n*-hexane and filtered. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, to give 0.50 g (74%) of the chloride.

3-(4-Methylphenoxy)propyl Bromide. 1,3-Dibromopropane (1.35 g, 6.7 mmol) was added to a DMSO solution (10 mL) of 4-cresol (0.6 g, 6.7 mmol) and powdered KOH (0.55 g, 8.3 mmol, 85% purity). The mixture was stirred for 4 h at room temperature, poured into water, and extracted with *n*-hexane. The *n*-hexane layer was washed with 1 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure, to give 1.00 g (60%) of the bromide.

(4-Methylphenoxy)ethyl Bromide. A mixture of 10 mL of water, 4-cresol (2.0 g, 19 mmol), and dibromoethane (3.48 g, 19 mmol) was stirred and heated to boiling. To the boiling solution was added dropwise a solution of NaOH (0.96 g, 24 mmol) in 3 mL of water. The mixture was refluxed for 2 h, poured into water, and extracted with *n*-hexane. The organic layer was washed with 1 N NaOH and water, dried over $MgSO_4$, and evaporated to dryness under reduced pressure, to give 1.95 g (49%) of the bromide.

4-(2-Ethylbutyl)phenyl 4-Butylbenzyl Ether (26). 4-Butylbenzyl chloride (0.56 g, 3.1 mmol) was added to a DMSO solution (5 mL) of 4-(2-ethylbutyl)phenol (0.5 g, 2.8 mmol) (Hayashi et al., 1989) and 0.28 g of powdered KOH (0.28 g, 4.3 mmol, 85% purity). The mixture was stirred for 2 h at 60 °C, dissolved in 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 5% ethyl acetate in *n*-hexane, yielding 0.69 g (76%) of the ether as an oil: ^{1}H NMR (ppm, $CDCl_3$) δ 7.20 (m, 4 H, C_6H_4), 6.92 (m, 4 H, C_6H_4), 4.93 (s, 2 H, OCH_2), 2.60 (t, J = 6 Hz, 2 H, $ArCH_2$), 2.47 (d, J = 5 Hz, 2 H, $ArCH_2$), 1.27 (m, 9 H), 0.90 (t, J = 6 Hz, 3 H, CH_3), 0.87 (t, J = 6 Hz, 6 H, CH_3).

Compounds **1–25** and **27–45** were prepared from an appropriate 4-substituted phenol and phenylalkyl or phenoxyalkyl halide by a method analogous for the preparation of **26**. The 4-substituted phenols used for the preparation of **17** and **41–45** have been reported previously (Hayashi et al., 1989).

4-[4-(2-Ethylbutyl)phenoxy]phenol. A mixture of 4-(2-ethylbutyl)phenol (1.5 g, 8.4 mmol), 4-bromoanisole (1.73 g, 9.3 mmol), K_2CO_3 (1.51 g, 10.9 mmol), and a catalytic amount of CuI was stirred for 12 h at 160–170 °C. After the mixture was cooled, *n*-hexane was added and the insoluble material was filtered off. The filtrate was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness, giving 2.00 g (84%) of 4-[4-(2-ethylbutyl)phenoxy]-anisole as an oil.

To this anisole was added pyridine hydrochloride (10 g), and the mixture was heated for 3 h at 200 °C. After being cooled to room temperature, the mixture was diluted with water and treated with diethyl ether. The ether layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by a silica gel column that was eluted with 20% ethyl acetate in *n*-hexane, to give 1.34 g (73%) of 4-[4-(2-ethylbutyl)phenoxy]phenol.

4-(2-Ethylbutyl)phenyl 4-Ethoxyphenyl Ether (46). Ethyl bromide (0.18 g, 1.7 mmol) was added slowly to a DMSO solution of 4-[4-(2-ethylbutyl)phenoxy]phenol (0.4 g, 1.5 mmol) and powdered KOH (0.15 g, 2.3 mmol, 85% purity). The mixture was stirred for 30 min at room temperature, poured into water, and extracted with *n*-hexane. The *n*-hexane layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography with 5% ethyl acetate in *n*-hexane as solvent, yielding 0.20 g (45%) of 4-[4-(2-ethylbutyl)-phenoxy]phenoxyethane: ^{1}H NMR (ppm, $CDCl_3$) δ 6.90 (m, 4 H, C_6H_4), 6.87 (m, 4 H, C_6H_4), 4.92 (s, 2 H, OCH_2), 3.90 (s, 3 H, OCH_3), 2.43 (d, J = 6 Hz, 2 H, $ArCH_2$), 1.25 (m, 5 H), 0.87 (t, J = 6 Hz, 6 H, CH_2CH_3).

By methods analogous to the preparation of compound **46**, compounds **47–49** were prepared from 3- or 4-[4-(2-ethylbutyl)-phenoxy]phenol and ethyl or propyl bromide.

1-Methyl-2-[4-(2-ethylbutyl)phenoxy]ethanol. A DMSO solution of 4-(2-ethylbutyl)phenol (0.6 g, 3.4 mmol), propylene oxide (0.23 g, 4.0 mmol), and powdered KOH (0.33 g, 5.0 mmol, 85% purity) was stirred for 6 h at 60 °C. The mixture was dissolved in water, treated with diethyl ether, washed with 1 N NaOH and water, and dried over $MgSO_4$. The ether layer was concentrated under reduced pressure to give 0.67 g (84%) of 1-methyl-2-[4-(2-ethylbutyl)phenoxy]ethanol as an oil.

4-Neopentylphenyl 2-(2-Pyridyloxy)ethyl Ether (61). To a suspension of NaH (0.12 g, 3.0 mmol, 60% oil suspension) in 5 mL of dimethylformamide (DMF) was added slowly a solution of (4-neopentylphenoxy)ethanol (0.5 g, 2.4 mmol), which was prepared from 4-neopentylphenol (Hayashi et al., 1989) and ethylene bromohydrine, in 2 mL of DMF. After bubbling ceased, 2-chloropyridine (0.30 g, 2.6 mmol) was added slowly to the solution and stirred for 5 h at 100 °C. The mixture was 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 purified by silica gel column chromatography with 10% ethyl acetate in *n*-hexane, to yield 0.50 g (73%) of pyridine: ^{1}H NMR (ppm, $CDCl_3$) δ 8.07 (m, 1 H, C_5NH_4), 6.93 (m, 7 H, ArH), 4.40 (m, 4 H, OCH_2CH_2), 2.40 (s, 2 H, $ArCH_2$), 0.88 (s, 9 H, CH_3).

Compounds **50–57**, **60**, and **62–64** were prepared from an appropriate 4-substituted phenoxyalkanol and chloropyridine by a method analogous to the preparation of **61**.

4-(2-Ethylbutyl)phenyl 2-(3-Pyridyloxy)ethyl Ether (58). To a suspension of NaH (0.15 g, 3.3 mmol, 53% oil suspension) in 5 mL of hexamethylphosphoramide (HMPA) was added slowly a solution of 3-hydroxypyridine (0.28 g, 2.9 mmol) in 1 mL of HMPA. After bubbling ceased, 4-(2-ethylbutyl)phenoxyethyl bromide (0.6 g, 2.9 mmol), which was prepared from 4-(2-ethylbutyl)phenol and 1,2-dibromoethane, in 1 mL of HMPA was added slowly, and the solution was stirred for 3 h at room temperature. The mixture was poured into water 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 10% ethyl acetate in *n*-hexane, to yield 0.38 g (60%) of pyridine: ^{1}H NMR (ppm, $CDCl_3$) δ 8.28 (m, 2 H, C_5NH_4), 7.20 (m, 2 H, C_5NH_4), 6.95 (m, 4 H, C_6H_4), 4.30 (s, 4 H, OCH_2CH_2), 2.47 (d, 2 H, J = 6 Hz, $ArCH_2$), 1.27 (m, 5 H), 0.87 (t, 6 H, J = 6 Hz, CH_3).

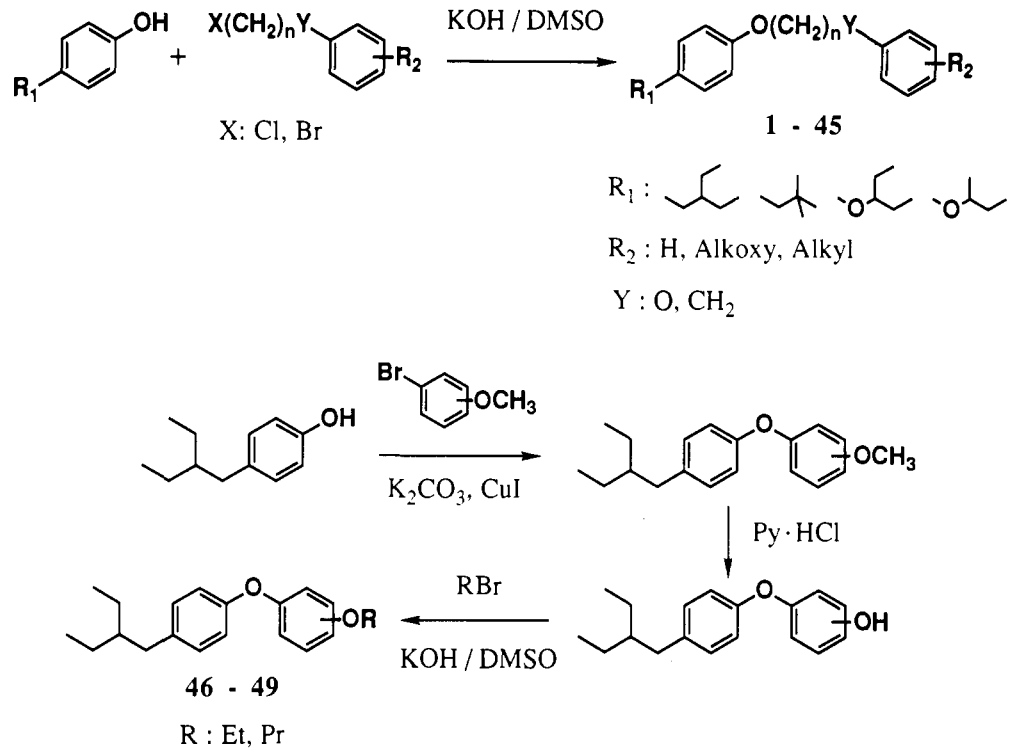
By an analogous method, compound **59** was prepared by using 4-hydroxypyridine in place of 3-hydroxypyridine.

6-Methoxy-3-picolyl Bromide. To a 10-mL portion of sodium methylate (28% in methanol) was added 6-bromo-3-picoline (2.0 g, 12 mmol). The mixture was heated to reflux for 6 h, poured into water, and extracted with diethyl ether. The diethyl ether layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving 1.24 g (96%) of 6-methoxy-3-picoline as an oil.

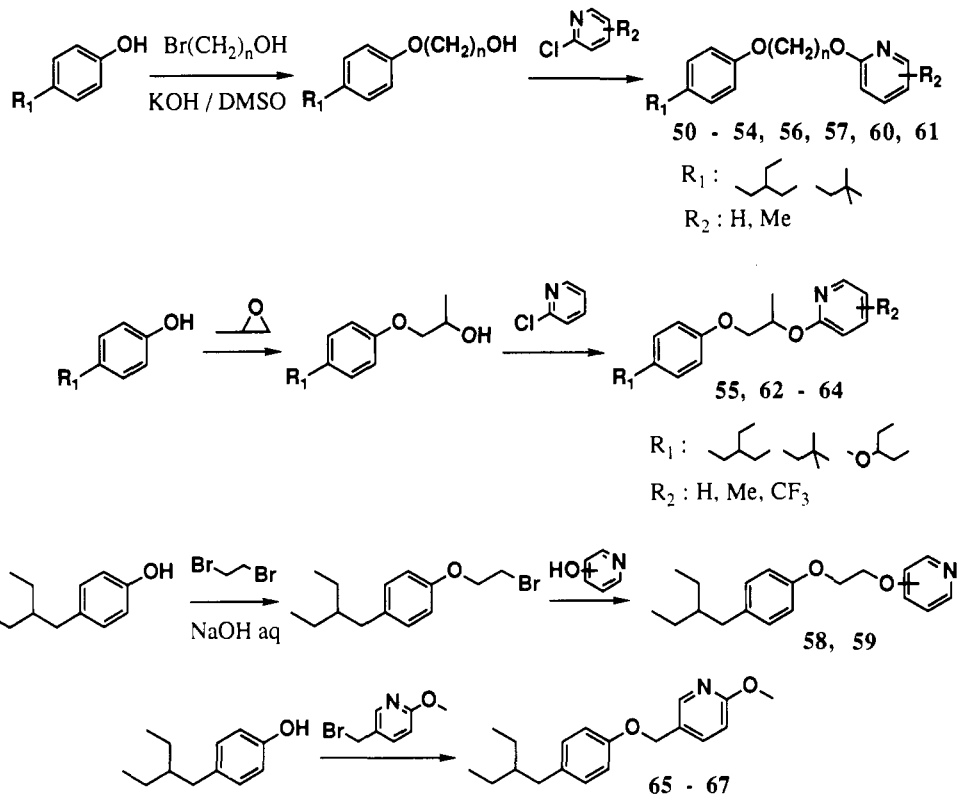
A carbon tetrachloride solution (10 mL) of 6-methoxy-3-picoline (1.24 g, 10 mmol), *N*-bromosuccinimide (2.06 g, 12 mmol), and benzoyl peroxide (0.09 g, 0.4 mmol) was refluxed for 3 h. The mixture was filtered, and the organic filtrate was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was put on a silica gel column chromatographed with 10% ethyl acetate in *n*-hexane, to give 1.08 g (46%) of 6-methoxy-3-picolyl bromide.

4-(2-Ethylbutyl)phenyl 6-Methoxy-3-picolyl Ether (67). 6-Methoxy-3-picolyl bromide (1.00 g, 5.0 mmol) was added to a DMSO solution (5 mL) of 4-(2-ethylbutyl)phenol (0.87 g, 4.9 mmol) and powdered KOH (0.48 g, 7.3 mmol). The mixture was stirred overnight at 60 °C, dissolved in 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 5% ethyl acetate in *n*-hexane, yielding 1.10 g (74%) of the ether as oil: ^{1}H NMR (ppm, $CDCl_3$) δ 8.13 (d, J = 2 Hz, 1 H, C_5NH_4), 7.00 (m, 6 H, ArH), 4.92 (s, 2 H, OCH_2), 3.90 (s, 3 H, OCH_3), 2.43 (d, J = 6 Hz, 2 H, $ArCH_2$), 1.25 (m, 5 H), 0.87 (t, 6 H, CH_3).

Scheme I



Scheme II

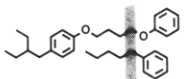
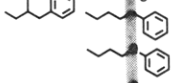


Compounds **65** and **66** were prepared by a method analogous to the preparation of **67**.

The reaction pathways are summarized in Schemes I and II. All of the final compounds listed in Tables I and II are either oils or glasses at room temperature. The identification of the molecular formula was made by elemental analyses for C, H, and N within the error of ±0.3%.

Bioassay Procedure. Fourth larval instars of *C. 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 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 replications at which high ratings (usually more than 50% inhibition of metamorphosis) were recorded, but experiments usually were

Table I. Structure and Activity against *C. pipiens* of 4-Substituted-Phenyl Phenylalkyl and Phenoxyalkyl Ethers[a]

	Structure	pI_{50}[b]	D[c]
1		—	22.06
2		4.24	20.95
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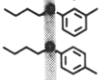
4		6.48	21.90
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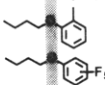
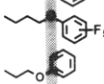
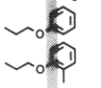
6		5.11	20.38
7		—	21.35
8		7.15	19.55
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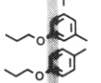
10		7.17	20.77
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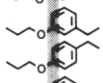
12		7.58	22.06
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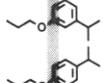
14		7.78	22.06
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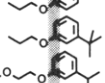
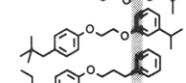
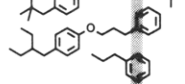
16		—	22.06
17		7.88	20.77
18		6.70	19.73
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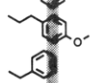
20		4.96	20.70
21		6.80	20.52
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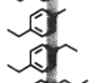
23		8.03	18.42
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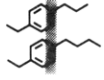
25		8.07	20.73
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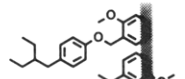
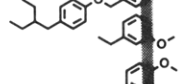
27		—	17.20
28		6.90	19.55
29		8.52	19.53
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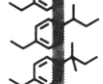
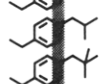
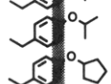
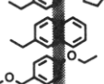
31		6.80	22.04
32		8.80	19.71
33		8.18	19.71
34		8.24	20.93
35		7.35	20.93
36		8.33	20.93
37		6.45	20.93
38		9.04	20.76
39		6.72	21.69
40		6.90	18.98
41		7.62	19.47
42		7.58	19.47
43		6.96	19.30
44		7.12	20.58
45		7.61	20.58
46		5.07	19.13
47		5.19	19.31
48		5.13	20.34
49		5.26	20.63
	JH I	6.29	
	methoprene	9.50	
	fenoxycarb	8.82	

[a] Shadowing shows the δ-position or the site about δ from the central oxygen atom. [b] The logarithm of reciprocal of the molar concentration at which 50% inhibition of metamorphosis is observed. [c] The overall length of the molecule defined in Figure 2.

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.

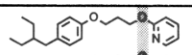
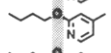
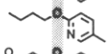
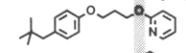
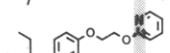
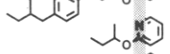
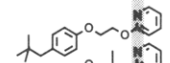
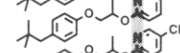
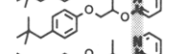
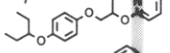
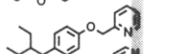
The activity was expressed in terms of pI_{50} (molar), the logarithm of the reciprocal of the concentration at which 50% inhibition of metamorphosis is observed. The data are summarized in Tables I and II, together with those of JH I, methoprene, and fenoxycarb as references. JH I was purchased from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

RESULTS AND DISCUSSION

JH Activity and Structure. We first prepared the 4-substituted-phenyl phenylalkyl and phenoxyalkyl ethers (**1**–**49**) in Table I and then the corresponding pyridine compounds (**50**–**67**) in Table II. The 4-substituent was in most of the compounds confined to 4-(2-ethylbutyl)-phenyl, since this substructure was important in conferring high activity in the previous 4-substituted-phenoxyalkanaldoxime *O*-ether series of compounds (Hayashi et al., 1989). The length of the chain that connects the central (4-substituted)phenoxy oxygen atom and the benzene or pyridine ring at the other end were varied so as to examine the positional effect of the aromatic function. In the previous oxime, ether, and hydroxylamine compounds, the activity has been shown to be highest when an appropriate heteroatom is located at the δ-position from the central oxygen atom (Niwa et al., 1989, 1990; Hayashi et al., 1989). The δ-position or the site about δ from the central oxygen atom in this set of compounds is indicated by shadowing in Tables I and II.

It has also been shown in classes of JH-active compounds that the steric dimensions, especially the overall length of the molecules, are of prime importance for the expression of the JH activity (Nakayama et al., 1984; Niwa et al., 1988, 1989, 1990; Hayashi et al., 1989). We thus considered this factor as well. Figure 2 explains the total length of the molecules (*D*). It was measured in the extended or energy minimum conformation along the axis that passes through the central oxygen atom with an angle of 40.02° to the bond that connects the ether oxygen atom and aralkyl or aralkyloxyalkyl moiety (Hayashi et al., 1989). The molecules were constructed by the CPK model according to the torsion angles given by the energy minimum conformation estimated by using AMPAC (QCPE No. 523) with AM1 parameterization (Dewar et al., 1985; Dewar and Stew-

Table II. Structure and Activity against *C. pipiens* of 4-Substituted-Phenyl Pyridylalkyl and Pyridyloxyalkyl Ethers[a]

	Structure	pI_{50}[b]	D[c]
50		8.44	20.78
51		7.63	21.90
52		7.88	21.66
53		8.22	19.47
54		10.04	19.55
55		9.64	19.55
56		7.80	20.77
57		9.10	20.77
58		6.73	19.55
59		5.04	19.55
60		8.69	19.55
61		9.34	18.27
62		8.72	18.27
63		7.45	20.01
64		7.92	19.38
65		4.93	17.20
66		5.70	17.20
67		7.94	19.53

[a-c] See footnotes *a-c* of Table I.

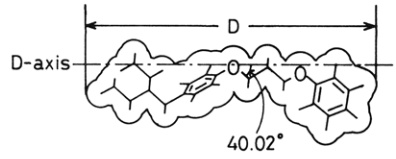


Figure 2. Definition of length parameter *D*. The model compound is 4-(2-ethylbutyl)phenyl phenylpropyl ether. The ends of the bars of the structure represent hydrogen atoms.

art, 1986), and the values were calculated with a computer program devised for the estimation of *D* and related dimensional parameters (Asao and Iwamura, 1985). The results are shown in Tables I and II, together with the pI_{50} values against *C. pipiens*. In the previous sets of compounds mentioned above, the most favorable length for activity has been estimated to be 21–22 Å.

Phenylalkyl and Phenoxyalkyl Ethers. Phenoxybutyl compound **1** showed little activity within the concentration range tested. Incidentally, it does not have a heteroatom at the δ-position, and the terminal bulkiness due to the benzene ring may work disadvantageously. Compound **2** has no heteroatom but had signs of activity, though very poor. (3-Methylphenoxy)propyl **4** and its 4-methyl congener **5** apparently have a heteroatom, oxygen, at the right, δ-place, and about the right length. Still, their potency was weak. The shorter, unsubstituted phenoxy **3** showed a little more potency than these.

The phenoxyethyl series of compounds **8–16** has the oxygen atom at γ from the central oxygen atom, the position one methylene unit out of the correct place. Nevertheless, they had activity as high as that of the δ-oxygenous phenoxypropyl compounds **3–6**. The effects of substitution on the benzene ring were apparently anomalous with respect to the length *D* vs activity relationship. 3-Methyl **10** was about 10 times more potent than 4-methyl **11**, irrespective of the fact that they have the same *D* (21 Å). 2-Methyl **9** was impotent, but the compound of the same *D*, unsubstituted **8**, was as potent as **10**. The activity of 3-ethyl **12** was about 100 times higher than that of 4-ethyl **13**, and this also cannot be explained simply by the *D* values; the length of both compounds is the same in terms of *D*. The comparative activity of 3-isopropyl **14** to 3-ethyl **12** suggests that one methyl branch in the 3-substituent is at least not detrimental, but if doubly branched, it is fatal to activity as seen by the impotency of *tert*-butyl **16**. Incidentally, they have the same *D* (22.06 Å). At the 4-position, a single branching was sufficient to make compound **15** impotent irrespective of the fact that it has about the correct *D* like 4-ethyl **13**. These results are considered to show that steric effects other than *D* effects are operating in these compounds. The 4-neopentyl compound **17** was as potent as its 4-(2-ethylbutyl)phenyl congener **14**. The nonoxygenous phenylpropyl **18** was only slightly less active than the corresponding, δ-oxygenated, phenoxyethyl **8**.

In the phenethyl compounds **19–21**, the δ-position is buried somewhere in the benzene moiety. The activity of 4-methoxy **21**, whose *D* is about optimum, was higher than the potency of the shorter, unsubstituted **19**, but that of 3-methyl **20**, whose *D* is also about optimum, was lower. Thus, the activity values are not in line with the *D* value, and the steric effects other than the *D* effects are again suggested to be operating.

If the measure as to the site of the position-specific, heteroatom interaction is applied as it stands to the benzyl ethers **22–45**, it is thought to be at somewhere around the right edge of the benzene moiety. In this series of compounds, the *D* vs activity relationship was systematically examined. In the 4-alkylbenzyl compounds **22–26**, the most active was 4-ethyl **24** with the *D* value of 19.7 Å. 4-*n*-Propyl **25** and 4-*n*-butyl **26** that are supposed to have a favorable *D* (21–22 Å) were less potent. A similar trend was also observed for the 4-alkoxybenzyl derivatives **29–31**. The activity of 4-*n*-propoxy **31** with the *D* value of 22 Å was somewhat lower than that of 4-methoxy **29** with the value of 19.5 Å, and the potency of **29** was comparable to that of 4-ethoxy **30**, whose *D* value (20.8 Å) is near the lower edge of the optimum range. These results suggest that the optimum length is somewhat shorter than that observed for the previous, nonaromatic classes of compounds, so far as it is examined by *D*. The far smaller potency of 3-methoxy **28** compared to that of the corresponding 4-methoxy **29** is attributable to steric factors other than *D*. An unfavorable steric torsion is a possibility for the impotency of 2-substituted **27** compared with the activity of unsubstituted **22** having the same *D* value.

The branched, 4-isopropylbenzyl compound **32** was active, the pI_{50} value being several to 10 times less than that of methoprene but as high as that of fenoxycarb [ethyl *N*-(4-phenoxyphenoxy)ethylcarbamate] (Fischer et al., 1980), another highly active JH mimetic. Compound **32** is the entity that apparently has no heteroatom but still has a fairly high potency. Through the benzyl subseries, 4-isopropoxybenzyl **38** had the highest potency, pI_{50} being slightly larger than that of **32**. The alteration of the 4-(2-ethylbutyl) substituent at another end resulted in the less potent compounds **41–45**.

The potency of the phenyl ethers **46–49** was not at all conspicuous. This seems to be due to the fact that their molecular dimensions or molecular shape are greatly deviated from those of the active series of compounds.

Pyridylalkyl and Pyridyloxyalkyl Ethers. The potency

of (2-pyridyloxy)propyl compounds **50–52** in Table II was about 10 times higher than that of the corresponding phenoxypropyl derivatives **3–5**. (2-Pyridyloxy)ether **54** was highly active, the pI_{50} value being larger than that of methoprene, and the potency of 2-(2-pyridyloxy)propyl ether congener **55** was at the methoprene level. The potency of 5-methylpyridyloxy analogue **57** was about 10 times less than that of the unsubstituted **54**, and 6-methyl **56** was far poorer. The situation was not in accord with that observed for the corresponding phenoxypropyl derivatives 10 and 11, *p*-methyl 11 that corresponds to 5-methyl **57** being far less potent than *m*-methyl 10 that corresponds to 4-methyl **56**. This may suggest that electrostatic or conformational properties of pyridines are different from those of benzene congeners. The far lower potency of the N-positional isomers, 3- and 4-pyridyloxy **58** and **59**, may be also attributable to a similar cause, and the relatively better pyrimidine analogue **60** suggests the importance of the *o*-aza structure for activity. 4-Neopentyl- and 4-(2-ethylpropoxy)phenyl ethers **61–64** were prepared, but they did not exceed in activity the 4-(2-ethylbutyl) series of compounds. The potency of picolyl **65–67** was considerably lower than that of the pyridyloxyethyl series.

Through the study of the types of compounds, it was suggested that the electrostatic and steric effects are dependent on both the structure and position of the aromatic function.

Conclusions and Prospects. We developed 4-alkylphenyl phenylalkyl and phenoxyalkyl ethers and the corresponding pyridylalkyl and pyridyloxyalkyl ethers as a new class of JH-active compounds. The most active one in the former benzene series was 4-(2-ethylbutyl)phenyl 4-isopropylbenzyl ether (**38**), the pI_{50} value against common mosquitoes being 9.0, and that in the pyridine series was 4-(2-ethylbutyl)phenyl 2-(2-pyridyloxy)ethyl ether (**54**), the pI_{50} being 10.0. The design of the molecules was based on the hybridization of the structure of our previous (4-alkylphenoxy)alkanaldoxime *O*-ethers (Hayashi et al., 1989) and those of reportedly active 4-phenoxyphenyl benzyl ethers (Karrer and Farooq, 1980) and (4-phenoxyphenoxy)-alkyl pyridyl ethers (Ohsumi et al., 1985).

Through the structure–activity studies of a variety of JH-active compounds (Nakayama et al., 1984, 1985; Niwa et al., 1988, 1989, 1990; Hayashi et al., 1989), the common structural features that are important for conferring high JH activity have been suggested to be the overall molecular dimension and a position-specific functional effect. The functions studied there have been oxime, ether, hydroxylamine, and amine. This set of compounds has, however, a bulky and electrostatically unique aromatic ring in place of the nonaromatic functions, and examination of their structure–activity profiles with reference to the previous nonaromatic compounds brought seemingly different profiles into relief.

The structure–overall length (*D*) relation was not necessarily in order. Moreover, the position-specific interaction site suggested previously seemed obscure. The most active member of this class, 2-pyridyloxyethyl compound **54**, has about 1.5 Å shorter *D* than its optimum (21–22 Å). The position-specific heteroatom interaction site that is thought to be at δ from the central oxygen atom is not found in these compounds, the pyridyloxy oxygen atom being at the γ-position and the δ-site being buried in the aromatic ring. The δ-oxygen congeners, 2-pyridyloxypropyl **50–52**, were less potent, although they have about the right *D*. Conspicuously, the benzene congener of **54**, compound **8**, was not the most potent member in the benzene subseries, which was compound **38**. This compound has a pertinent *D* but the site of point interaction is obscure, being buried somewhere in the benzene region. The potency of the seemingly δ-oxygenous **3–6** was not necessarily higher than that of the γ-oxygenous series of compounds having a similar *D*. The situations were further complicated by introducing a substituent at positions of the aromatic rings.

Efforts are obviously necessary to find explanations for this situation that do not conflict with the previously accumulated knowledge. A likelihood is that the aromatic moiety substitutes in the role of heteroatom of the nonaromatic series of compound and the steric characteristics are greatly influential on activity. In the past, a number of geranyl phenyl ether type compounds have been developed and shown to be active to various extents against species of insect (Henrick, 1982). Though their overall structure is different from that of the present compounds, the molecules have in common an aromatic function at one end, and thus the problems raised here may be shared by them as well. In the paper that follows this one (Hayashi et al., 1990), we explore the electrostatic features of the aromatic functions built in this series of compounds in reference to the nonaromatic ones and on the basis of this elucidate their structural profiles that govern the activity. In essence, the fundamental structural conditions for JH activity were in common.

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Supplementary Material Available: Table of analytical data for 4-alkylphenyl phenylalkyl, phenoxyalkyl, pyridylalkyl, and pyridyloxyalkyl ethers (3 pages). Ordering information is given on any current masthead page.

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