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

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

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

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

ACKNOWLEDGMENT

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

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

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

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

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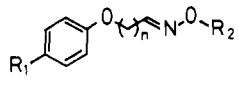


R_1 = Alkoxy, Alkyl

R_2 = Et, n-Pr, i-Pr

n = 1, 2

Figure 1. Generic formulas of the compounds studied.

was replaced by a variety of alkoxy and alkyl groups, with the aim of further exploring the structural conditions for high potency of this part of the molecules and of developing new JH-active compounds. We obtained 3-(4-isobutylphenoxy)-, 3-[4-(2-ethylbutyl)phenoxy]-, and 3-(4-neopentylphenoxy)propionaldoxime *O*-isopropyl ethers (**35**, **37**, **39**), the activity of which against *Culex pipiens* was as high as that of the previously developed 3-[4-(3-methylphenoxy)phenoxy]propionaldoxime *O*-isopropyl ether (Niwa et al., 1988) and 3-[4-(3-methylphenoxy)-phenoxy]propyl isobutyl ether (Niwa et al., 1989), which are the most active of the JH mimics known so far against this mosquito. The quantitative structure–activity relationship of the set of the compounds was analyzed to predict the potency from the structural factors. Figure 1 shows the generic formula of the compounds studied here.

EXPERIMENTAL SECTION

^{1}H NMR spectra were obtained in CCl_4 or $CDCl_3$ with tetramethylsilane as the internal reference in a JEOL PMX-60 spectrometer. IR spectra were recorded on a Shimadzu IR-27G spectrometer.

4-Alkoxyphenols. An appropriate alkyl halide (9 mmol) was added slowly to a Me_2SO solution (30 mL) of hydroquinone (1.5 g, 13.6 mmol) and powdered KOH (1.4 g, 21 mmol). The mixture was stirred for 3 h at 50–60 °C, poured into water, and extracted with benzene. The benzene layer was extracted with 1 N NaOH, and the aqueous layer was first acidified by concentrated HCl and then extracted with benzene. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving an oily product.

(4-Hydroxyphenoxy)acetaldoxime Diethyl Acetal. Bromoacetaldehyde diethyl acetal (6.0 g, 30.5 mmol) was added slowly to a Me_2SO solution (130 mL) of hydroquinone (5.0 g, 45.5 mmol) and powdered KOH (3.0 g, 45.5 mmol, 85% purity). The mixture was stirred for 12 h at 50 °C, poured into water, and extracted with benzene. The benzene layer was extracted with 1 N NaOH, and the aqueous layer was first acidified by concentrated HCl and then extracted with benzene. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving 3.3 g (48%) of the acetal as oil.

(4-Hydroxyphenoxy)acetaldoxime *O*-Propyl Ether. An aqueous solution (10 mL) of *O*-propylhydroxylammonium chloride (2.0 g, 18 mmol) and 6 N HCl (0.2 mL) was added to (4-hydroxyphenoxy)acetaldehyde diethyl acetal (3.2 g, 14 mmol) in ethanol (70 mL). The mixture was stirred for 12 h at 50 °C, diluted with water, and extracted with benzene. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving 2.9 g (98%) of the ether as an oil.

(4-Alkoxyphenoxy)acetaldehyde Diethyl Acetal. By a method analogous to the preparation of the corresponding 4-hydroxy compounds, bromoacetaldehyde diethyl acetal (1.3 g, 6.6 mmol) and an appropriate 4-alkoxyphenol were reacted to give the product as an oil.

3-(4-Alkoxyphenoxy)propionaldehyde Diethyl Acetal. By a method analogous to the preparation of the corresponding acetaldehyde diethyl acetal, 3-chloropropionaldehyde diethyl acetal and an appropriate 4-alkoxyphenol was reacted to give an oily product.

(4-Alkoxyphenoxy)acetaldoxime *O*-Propyl Ethers 1–21. *A. From (4-Alkoxyphenoxy)acetaldehyde Diethyl Acetal.* Compounds **1**, **2**, **12**, and **21** were prepared by a method analogous to the preparation of 4-hydroxyacetaldoxime *O*-propyl ether from *O*-propylhydroxylammonium chloride and an appropriate acetal. The product was purified by silica gel column chromatography with 10% *n*-hexane in benzene as solvent.

B. From (4-Hydroxyphenoxy)acetaldoxime O-Propyl Ether. Compounds **3–11** and **13–20** were prepared by a method analogous for the preparation of 4-alkoxyphenols from (4-hydroxyphenoxy)acetaldoxime *O*-propyl ether and an appropriate alkyl halide. The product was purified by silica gel column chromatography with 0–5% ethyl acetate in benzene as solvent.

3-(4-Alkoxyphenoxy)propionaldoxime *O*-Ethyl and *O*-Isopropyl Ethers 24–29. By analogy with the preparation of compounds **1**, **2**, **12**, and **21**, compounds **24–29** were prepared from an appropriate diethyl acetal and *O*-alkylhydroxylammonium chloride. The product was purified by silica gel column chromatography with 5% ethyl acetate in benzene as solvent.

Methoxides 22 and 30. The methoxy analogues **22** and **30** were prepared by methoxymercuration–demercuration of olefins **16** and **29**, respectively, according to the method of Wakabayashi (1969). A solution of mercuric acetate (0.5 g, 15 mmol) in methanol (20 mL) was added to a stirred, ice-cooled solution of the appropriate olefin (14 mmol) in methanol (10 mL). After the mixture was stirred for 1.5 h in an ice bath, a solution of KOH (0.3 g, 4.5 mmol) in methanol (10 mL) and then $NaBH_4$ (0.03 g, 0.8 mmol) were added. Stirring was continued for 1 h, and the supernatant was decanted from Hg, poured into water, and extracted with benzene. 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 5% ethyl acetate in benzene as solvent.

Epoxide 23. *m*-Chloroperbenzoic acid (0.2 g, 0.8 mmol) in dichloromethane (5 mL) was added slowly to a solution of **16** in dichloromethane (5 mL) at an ice-bath temperature. The mixture was stirred for 1 h at room temperature, shaken with an aqueous solution of 10% $NaHSO_3$ followed by an aqueous solution of 10% $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 5% ethyl acetate in benzene as solvent.

4-Acylanisoles. Anisole (2.5 g, 23 mmol) was added slowly to a mixture of dichloromethane (20 mL) and anhydrous $AlCl_3$. An acyl chloride (28 mmol) was then added to the mixture below 0 °C in an ice–salt bath. The mixture was stirred for 4 h at room temperature and poured into ice–water (60 g) to which 3 mL of concentrated HCl had been added. The organic layer was separated, washed with 1 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure, giving an oily product.

4-Alkylanisoles. A mixture of a 4-acylanisole (16 mmol), NaOH (2.0 g, 47 mmol), hydrazine hydrate (1.6 g, 32 mmol), and triethylene glycol (30 mL) was refluxed for 4 h at 150–160 °C. The mixture was cooled, poured into water, extracted with benzene, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene as solvent to give an oily product.

4-Alkylphenols. A mixture of a 4-alkylanisole (13 mmol) and pyridine hydrochloride (4.6 g, 40 mmol) was

heated for 3 h at 200 °C under stirring, cooled, poured into water, and then extracted with ether. The extract was washed with water, dried over $MgSO_4$, and concentrated under a reduced pressure. The residual product was purified by silica gel column chromatography with benzene–ethyl acetate (1:1, v/v) as solvent.

(4-Alkylphenoxy)acetaldehyde Diethyl Acetal and 3-(4-Alkylphenoxy)propionaldehyde Diethyl Acetal. An appropriate phenol (4.0 mmol) and bromoacetaldehyde diethyl acetal or 3-chloropropionaldehyde diethyl acetal (4.2 mmol) was reacted by a method analogous to the preparation of the corresponding 4-alkoxy compounds to give an oily product.

(4-Alkylphenoxy)acetaldoxime *O*-*n*-Propyl Ethers 31 and 32 and (4-Alkylphenoxy)propionaldoxime *O*-Isopropyl Ethers 33–44. By analogy with the method for the preparation of compounds **24–29**, compounds **31–44** were prepared by the reaction of an appropriate precursor acetal (2.0 mmol) with either *O*-*n*-propyl- or *O*-isopropylhydroxylammonium chloride (2.7 mmol). The product was purified by silica gel column chromatography with benzene as solvent.

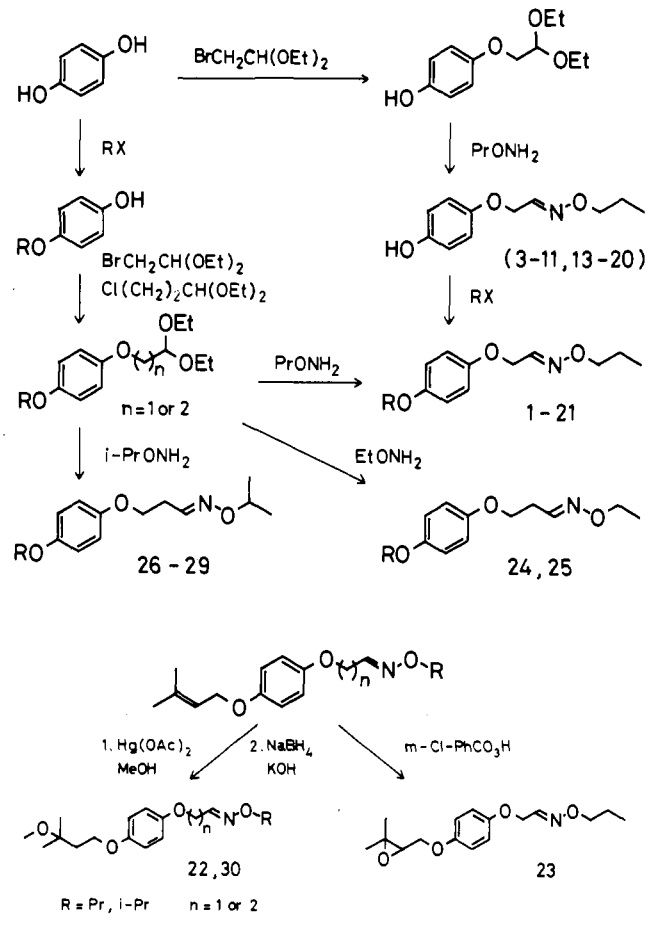
^{1}H NMR Spectra ($CDCl_3$; δ; *J*, Hz): Acetaldoxime moiety: (*E*)-α-H 7.47 (1 H, t, J = 6.0); (*Z*)-α-H 7.20 (1 H, t, J = 6.0); (*Z*)-β-H 4.73 (2 H, d, J = 4.0); (*E*)-β-H 4.53 (2 H, d, J = 6.0). Propionaldoxime moiety: α-H 7.43 (1 H, t, J = 6.0); β-H 2.70 (2 H, m); γ-H 4.03 (2 H, t, J = 6.0). *O*-Ether moiety: $OCH(CH_3)_2$ 4.30 (1 H, m); $OCH_2(CH_2)_nCH_3$ 4.03 (2 H, t, J = 6.0); $OCH_2CH_2CH_3$ 1.63 (2 H, m); OCH_2CH_3 1.23 (3 H, t, J = 7.0); $OCH(CH_3)_2$ 1.23 (6 H, d, J = 6.0); $OCH_2CH_2CH_3$ 0.93 (3 H, t, J = 6.0). 4-Alkoxy moiety: terminal CH_3 0.88–1.00 (3 H or 6 H, t or d, J = 6.0); $OCH_2(CH_2)_nCH_3$ or $OCH_2(CH_2)_nCH(CH_3)_2$ 1.33 (1 H–12 H, m); OCH_2 or $OCH<$ 3.50–4.57 (2 H or 1 H, t, d, s, or m); OCH_3 3.17–3.93 (3 H, s); $OCH(CH_3)_2$, $OCH(CH_3)C_2H_5$, or OCH_2CH_3 1.20–1.37 (3 H or 6 H, t, d or s); $-CH=CH_2$ 6.00 (1 H, m); $-CH=CH_2$ 5.30 (2 H, m); $-C\equiv CH$ 2.43 (1 H, s); $CH=C(CH_3)_2$ 5.13 (1 H, t, J = 6.0); $CH=C(CH_3)_2$ 1.77 and 1.70 (6 H, s); C_6H_{11} 1.60 (11 H, m); C_6H_5 (5 H, s); epoxy *H* 3.70 (1 H, t, J = 5.0); epoxy CH_3 1.37 and 1.32 (6 H, s). 4-Alkyl moiety: terminal CH_3 0.85–0.95 (3 H, 6 H, or 9 H, t, d, or s); $ArCH_2$ or ArCH 2.40–2.55 (1 H or 2 H, t, d, s, or m); CH_2-c-*Pr* 0.37 (4 H or 5 H, m); CH_2-c-*Hx* 1.57 (11 H, m); other methylenes and methynes 1.22–1.57 (m).

The reaction pathways were summarized in Schemes I and II. All of the final products listed in Tables I and II are either oil or glass 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%. In the synthesis of the oximes, both *E* and *Z* isomers were produced: The ratio was estimated to be about 1:1 from ^{1}H NMR examination (Nakayama et al., 1985; Niwa et al., 1988). The oximes could not be separated by conventional chromatographic technique, and thus the compounds listed in the tables were bioassayed as mixtures of both isomers.

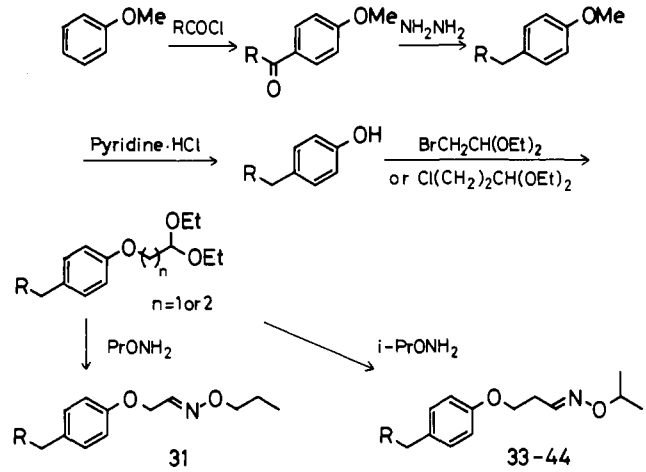
The extraction and chromatography with use of benzene as solvent were done in a well-ventilated hood. In consideration of the toxicity and carcinogenecity of benzene, it could be replaced by less toxic toluene in the extraction and by toluene or ethyl acetate in the chromatography.

Bioassay Procedure. Fourth larval instars of *Culex pipiens pallens* Coquillet were selected from colonies maintained at 28 °C in water containing a feed mixture of mouse food and dry yeast. The eggs were a gift of the Sumitomo Chemical Co., Ltd. Three batches of 20 larvae each were transferred to disposable plastic tumblers containing 100 mL of water. An ethanol solution (10 μL) of

Scheme I

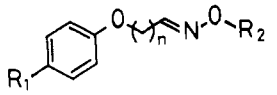


Scheme II



the test compounds was added to the tumblers, after which diet powder was added. The tumblers were covered with a transparent plastic cup 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 cuticle. The experimental results in the bioassays were confirmed mostly by replication at concentrations at which high ratings (usually more than 50% inhibition of metamorphosis) were recorded, but experiments usually were not repeated at concentration recorded for lower activity. When an abnormal rating was found, repetitions were made at that concentration and those near by. When more than one abnormal rating was obtained, the experiment was repeated for the entire concentration range. All the data,

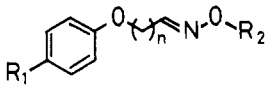
Table I. JH Activity and Physicochemical Parameters of (4-Alkoxyphenoxy)alkanaldoxime *O*-Ethers



no.	R_1	R_2	n	pI_{50}, M obsd	pI_{50}, M calcd	ΔpI_{50}	D^a	I_{br}(OR)	I_p
1	O-Me	*n*-Pr	1	5.13	5.41	−0.28	18.20	0.00	0.00
2	O-Et	*n*-Pr	1	5.27	5.98	−0.71	19.42	0.00	0.00
3	O-*n*-Pr	*n*-Pr	1	6.82	6.36	0.46	20.71	0.00	0.00
4	O-*n*-Bu	*n*-Pr	1	6.39	6.48	−0.09	21.93	0.00	0.00
5	O-*n*-pentyl	*n*-Pr	1	6.21	6.38	−0.17	23.21	0.00	0.00
6	O-*n*-Hx	*n*-Pr	1	5.46	6.05	−0.59	24.44	0.00	0.00
7	O-*n*-heptyl	*n*-Pr	1	5.29	5.48	−0.19	25.72	0.00	0.00
8	O-*n*-octyl	*n*-Pr	1	5.29	4.72	0.57	26.92	0.00	0.00
9	O-*i*-Pr	*n*-Pr	1	7.81	7.53	0.28	19.42	1.00	0.00
10	O-*i*-Bu	*n*-Pr	1	6.25	6.36	−0.11	20.71	0.00	0.00
11	O-isopentyl	*n*-Pr	1	6.79	6.48	0.31	21.93	0.00	0.00
12	O-*s*-Bu	*n*-Pr	1	7.57	7.90	−0.33	20.71	1.00	0.00
13	O-(1-Et)-*n*-Pr	*n*-Pr	1	7.83	7.90	−0.07	20.71	1.00	0.00
14	O-allyl	*n*-Pr	1	6.94	6.35	0.59	20.68	0.00	0.00
15	O-propargyl	*n*-Pr	1	6.20	6.30	−0.10	20.44	0.00	0.00
16	O-dimethylallyl	*n*-Pr	1	6.62	6.48	0.14	21.90	0.00	0.00
17	O-(3-OH)-*n*-Pr	*n*-Pr	1	6.79	6.48	0.31	21.75	0.00	0.00
18	O-EtOMe	*n*-Pr	1	5.90	6.48	−0.58	21.75	0.00	0.00
19	O-EtOEt	*n*-Pr	1	6.48	6.41	0.07	23.04	0.00	0.00
20	O-CH_2-c-Hx	*n*-Pr	1	6.66	6.48	0.18	22.11	0.00	0.00
21	O-benzyl	*n*-Pr	1	7.27	6.48	0.79	21.86	0.00	0.00
22	O-(3-Me-3-OMe)-*n*-Bu	*n*-Pr	1	5.77	6.41	−0.64	23.04	0.00	0.00
23	O-(2-epoxy-3-Me)-*n*-Bu	*n*-Pr	1	7.04	6.48	0.56	21.72	0.00	0.00
24	O-*n*-Pr	Et	2	7.91	7.52	0.39	20.62	0.00	1.00
25	O-*i*-Pr	Et	2	8.79	8.68	0.11	19.34	1.00	1.00
26	O-*i*-Pr	*i*-Pr	2	8.15	8.68	−0.53	19.34	1.00	1.00
27	O-*s*-Bu	*i*-Pr	2	9.18	9.07	0.11	20.62	1.00	1.00
28	O-(1-Et)-*n*-Pr	*i*-Pr	2	9.50	9.07	0.43	20.62	1.00	1.00
29	O-dimethylallyl	*i*-Pr	2	7.38	7.66	−0.28	21.81	0.00	1.00
30	O-(3-Me-3-OMe)-*n*-Bu	*i*-Pr	2	7.14	7.60	−0.46	22.95	0.00	1.00

[a] Key: *D*, the length in the fully extended conformation of the whole molecule along the axis that passes on the phenoxy oxygen atom and has an angle of 40.02° to its connecting bond to the oxime moiety; I_{br}(OR), indicator variable that takes 1 for the compounds having a branch at β of the 4-alkoxy substituents and 0 for others; I_p, indicator variable that takes 1 for propionaldoximes and 0 for acetaldoximes.

Table II. JH Activity and Physicochemical Parameters of (4-Alkylphenoxy)alkanaldoxime *O*-Ethers



no.	R_1	R_2	n	pI_{50}, M obsd	pI_{50}, M calcd	ΔpI_{50}	D^a	$\Delta T\beta$(R)	I_p
31	*n*-Bu	*n*-Pr	1	6.44	6.37	0.05	20.88	0.00	0.00
32	*n*-pentyl	*n*-Pr	1	6.02	6.48	−0.46	20.62	0.00	0.00
33	*n*-Pr	*i*-Pr	2	7.28	7.20	0.08	19.51	0.00	1.00
34	*n*-Bu	*i*-Pr	2	7.34	7.55	−0.21	20.79	0.00	1.00
35	*i*-Bu	*i*-Pr	2	10.85	10.48	0.37	19.51	1.25	1.00
36	*s*-Bu	*i*-Pr	2	6.73	7.20	−0.47	19.51	0.00	1.00
37	2-Et-*n*-Bu	*i*-Pr	2	10.76	10.84	−0.08	20.79	1.25	1.00
38	isopentyl	*i*-Pr	2	8.46	7.55	0.91	20.79	0.00	1.00
39	neopentyl	*i*-Pr	2	10.03	9.47	0.56	19.51	2.51	1.00
40	*tert*-pentyl	*i*-Pr	2	7.21	7.20	0.01	19.51	0.00	1.00
41	2-*n*-Pr-*n*-pentyl	*i*-Pr	2	9.78	9.93	−0.15	22.02	2.51	1.00
42	CH_2-c-Pr	*i*-Pr	2	8.71	9.45	−0.74	19.16	0.71	1.00
43	CH_2-1-Me-c-Pr	*i*-Pr	2	9.82	9.44	0.38	19.14	0.71	1.00
44	CH_2-c-Hx	*i*-Pr	2	9.37	9.82	−0.45	20.79	2.51	1.00
	JH I			6.29					
	methoprene			9.45					

[a] Key: *D* and I_p, see footnote *a*, Table I; $\Delta T\beta$(R), thickness at β-position of 4-alkyl substituents having a β-branch relative to the unbranched compounds.

excluding the abnormal value, were averaged. The percentage of the nonemergence controls (no chemicals added except 10 μL of ethanol) was less than 10% through the runs of the experiments.

The activity was expressed in terms of pI_{50} (M), the logarithm of the reciprocal of the concentration at which 50% inhibition of metamorphosis is observed. The data are summarized in Tables I and II, together with those of JH I [methyl (2*E*,6*E*)-*cis*-10,11-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate] and methoprene as references. JH I was purchased from Sigma Chemical Co., and methoprene was provided by Earth Chemical Co.

Table III. Development of Equation 2

const	$\Delta T\beta(R)^a$	$\Delta T\beta(R)^2$	$I_{br}(OR)$	I_p	D	D^2	s	r	$F_{x,y}{}^b$
6.90	4.75	−1.44					1.02	0.75	$F_{2,41}$ = 26.39
6.55	5.25	−1.59	1.86				0.76	0.87	$F_{1,40}$ = 33.62
6.23	4.02	−1.23	1.51	1.17			0.57	0.93	$F_{1,39}$ = 31.90
−29.24	4.34	−1.37	1.55	1.18	3.24	−0.07	0.46	0.96	$F_{2,37}$ = 12.50

[a] Squared correlation coefficients between parameters were as follows: $r(D, I_p) = 0.17$; $r(D, I_{OR}) = 0.07$; $r[D, \Delta T\beta(R)] = 0.03$; $r(I_p, I_{OR}) = 0.02$; $r[I_p, \Delta T\beta(R)] = 0.20$; $r[I_{br}(OR), \Delta T\beta(R)] = 0.03$. [b] F statistic for the significance of the addition of each variable (Benett and Franklyn, 1954).

RESULTS AND DISCUSSION

Development and JH Activity. The total length of the molecule is a basic and important factor for high JH activity (Nakayama et al., 1984, 1985; Niwa et al., 1988, 1989). Coincidentally, in the (4-*n*-alkoxyphenoxy)acetaldoxime *O*-propyl ethers **1**–**8**, *n*-propoxy **3**, and *n*-butoxy **4** had higher activity than that with shorter or longer *n*-alkoxys. Within this and similar length conditions, we prepared compounds with a branch(es), unsaturation, or heteroatom(s) to examine additional effects. Branching at the β-position to the benzene ring was found to enhance activity; that is, the activity of isopropoxy **9** was considerably higher than that of ethoxy **2** with the corresponding length, and similarly *s*-butoxy **12** and 1-ethylpropoxy **13** had significantly higher potency than *n*-propoxy **3**. On the basis of these results and the previously shown findings that, in the (4-phenoxyphenoxy)alkanaldoxime *O*-ether series of compounds, the potency of propionaldoximes is dozens of times higher than the corresponding acetaldoximes (Niwa et al., 1988), we prepared (4-alkoxyphenoxy)propionaldoxime **24**–**30**. The (4-*s*-butoxyphenoxy)- and [4-(1-ethylpropoxy)phenoxy]propionaldoxime *O*-isopropyl ethers **27** and **28** had the highest potency in the series and satisfied the necessary structural conditions mentioned above. Moreover, they had an isopropyl group at the other end of the molecule; the introduction of a methyl branch into the oxime *O*-ether end has already been shown to be favorable for activity (Nakayama et al., 1985; Niwa et al., 1988).

An alkyl group may well be equivalent with respect to its expression of biological activity to an alkoxy with the same or similar steric dimensions; we next prepared the 4-alkyl series of compounds **31**–**44**. Of these, (4-isobutylphenoxy)-, [4-(2-ethylbutyl)phenoxy]-, and (4-neopentylphenoxy)propionaldoxime *O*-isopropyl ethers **35**, **37**, and **39** had very potent activity, as high as that of the most potent members in the previous 4-phenoxyphenoxy series of compounds (Niwa et al., 1988). The branching effect at β to the aromatic ring appears to be more conspicuously displayed in this alkyl series of compounds than in the alkoxy compounds, the activity of isobutyl **35** and 2-ethylbutyl **37** being thousands of times higher than the corresponding *n*-propyl **33** and *n*-butyl **34**, respectively.

Quantitative Structure–Activity Relationship. Quantitative analysis was done stepwise of the 4-alkoxy and 4-alkyl series of compounds to identify the structural conditions common to both series as well as the different characteristics caused by the different structures.

Steric Parameters. To express the dimensional features of the molecule, we first defined the *D*-axis that passes through the phenoxy and oxime oxygen atoms in the fully extended conformation of the acetaldoxime *O*-ethers (Figure 2). By this definition, the angle between the *D*-axis and the bond that connects the phenoxy oxygen atom to the oxime moiety is 40.02°. For the propionaldoxime *O*-ethers, the *D*-axis was drawn so as to pass through the phenoxy oxygen atom, satisfying this angle condition. In the extended conformation, the zigzag plane of the 4-substituent was placed on the same plane as that of the alkanaldoxime *O*-ether moiety. The central benzene ring can rotate fully, without affecting the definition and values of the dimensional parameters described below.

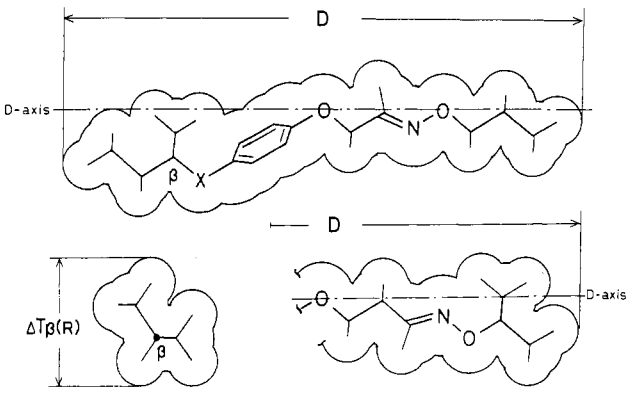


Figure 2. Definition of the steric parameters.

The length of the whole molecule was measured along the *D*-axis and named *D*. To express the bulkiness arising from the β-branch of the 4-substituents, we further defined $T\beta$ as the thickness at the β-position measured in the direction vertical to the zigzag plane. In the analysis, the value relative to the unbranched compounds $\Delta T\beta$ was used. Other dimensional parameters were also considered for both the aromatic and oxime substituents, but they were not significant at all for the present set of compounds. The dimensional parameters have been shown to be of utility in structure–activity relationship studies of earlier JH mimetics and of bitter amino acid and peptide derivatives (Asao et al., 1987). The values were calculated based on the CPK model with a computer program devised for the estimation of the *D* and related parameters (Asao and Iwamura, unpublished results).

Analysis. First, analysis was done of the alkoxy compounds **1**–**30**, giving eq 1 as the best correlation.

$$\underset{}{pI_{50}} = \underset{(1.51)}{3.40D} - \underset{(0.03)}{0.08D^2} + \underset{(0.44)}{1.12I_p} + \underset{(0.49)}{1.59I_{br}(OR)} - \underset{(16.94)}{31.06} \quad (1)$$

$$n = 30,\ s = 0.46,\ r = 0.93,\ F_{4,25} = 41.65$$

In this and eq 2 that follows, n is the number of compounds, s is the standard deviation, r is the multiple correlation coefficient, and the figures in parentheses are the 95% confidence intervals.

The significance of *D* and its squared term reflects the existence of an optimum length for the activity of the molecule. I_p is the indicator variable, taken to be 1 for the propionaldoxime and 0 for the acetaldoxime. Its coefficient value, 1.1, overlaps with that (1.3) for the previous (4-phenoxyphenoxy)alkanaldoxime *O*-ethers within 95% confidence intervals (Niwa et al., 1988). The effect of the β-branch of the 4-alkoxy substituents was expressed by the indicator variable $I_{br}(OR)$, because the variation in the activity was rather uniform. The $I_{br}(OR)$ takes 1 for the compounds with a branch and 0 for the others, and the increase in potency is estimated to be 40-fold, on the average. The OR in parentheses indicates that the variable

is for the 4-alkoxy compounds.

Equation 1 for the alkoxy compounds could be used to explain the activity of the alkyl compounds with no branches, when the value of $I_{br}(OR)$ is taken to be 0. In a reflection of the rise in activity caused by the β-branch of the 4-substituent being more prominent in the alkyl series, the pI_{50} values of the compounds with this feature deviated significantly from the values calculated by eq 1 with $I_{br}(OR) = 1$. Moreover, the extent of deviation was dependent on the bulkiness of the branch. We found it to be the $\Delta T\beta$ that best explains the situation and thus formulated eq 2 for the whole set of compounds. The

$$pI_{50} = \underset{(1.35)}{3.24}D - \underset{(0.03)}{0.07}D32 + \underset{(0.35)}{1.18}I_p + \underset{(0.42)}{1.55}I_{br}(OR) + \underset{(0.96)}{4.34}\Delta T\beta(R) - \underset{(0.39)}{1.37}\Delta T\beta(R)^2 - \underset{(15.10)}{29.24} \quad (2)$$

$$n = 44,\ s = 0.46,\ r = 0.96,\ F_{6,37} = 72.92$$

letter R in parentheses after the $\Delta T\beta$ means that the term is for the 4-alkyl compounds. The $\Delta T\beta(R)$ was significant with its squared term, and the rest of the features were the same as those of eq 1. This reflects 4-alkyl compounds with an appropriate β-branch having thousands of times higher activity than those having no β-branch. The parameter values of each compound are listed in Tables I and II, and the development of the final eq 2 is shown in Table III.

Conclusions and Prospects. The replacement of the terminal aromatic moiety of the previous (4-phenoxyphenoxy)alkanaldoxime *O*-ether-type of compounds (Nakayama et al., 1985; Niwa et al., 1988) to alkoxys and alkyls gave a new class of JH mimics, the (4-alkoxyphenoxy)- and (4-alkylphenoxy)alkanaldoxime *O*-ethers. The optimum length of the whole molecule was estimated to be about 22 Å, which coincided well with these lengths postulated for terpenoid (Nakayama et al., 1984), (4-phenoxyphenoxy)alkanaldoxime *O*-ether (Niwa et al., 1988), and (4-phenoxyphenoxy)alkyl alkyl ether (Niwa et al., 1989) compounds. As in previous results (Niwa et al., 1988), the activity of the propionaldoximes was dozens of times higher than that of the corresponding acetaldoximes, suggesting that there was a position-specific interaction site on the surface of the JH receptor. These length and positional effects are thought to be at operate in a variety of JH-active derivatives (Henrick, 1982) as well as in the phenoxyphenoxy types of compounds (Karrer and Farooq, 1981; Ohsumi et al., 1985).

The effect of the β-branch of the 4-substituents was to increase activity, especially in the 4-alkyl series of compounds. The introduction of an appropriate branch may make the conformation of the molecule more suitable for its accommodation to the receptor in the alkyl series than in the alkoxy. The difference probably reflects a subtle difference in the modes of binding of the two series of compounds and is attributable to the different atom species that connect the 4-substituents to the benzene moiety. The accumulation of information about the effects of local structures will help in further construction of new and highly active JH-mimetic compounds within the framework indicated by the optimum *D*.

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Supplementary Material Available: Table of analytical data for (4-alkoxyphenoxy)- and (4-alkylphenoxy)alkanaldoxime *O*-ethers (2 pages). Ordering information is given on any current masthead page.

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