Development of (Phenoxyphenoxy)- and (Benzylphenoxy)alkanaldoxime *O*-Ethers as Potent Insect Juvenile Hormone Mimics and Their Quantitative Structure–Activity Relationship

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We prepared a series of (4-phenoxyphenoxy)- and (4-benzylphenoxy)acetaldoxime *O*-ethers intending to develop compounds of high activity that mimic insect juvenile hormones (JHs). Their activity against a mosquito, *Culex pipiens*, was usually more than 100 times that of the terpenoid undecen-2-one oxime *O*-ethers we have already developed. On the basis of these results, structures with more activity were explored to obtain the corresponding propionaldoxime *O*-ethers series of compounds. The most active member of the class, 3-[4-(3-methylphenoxy)phenoxy]propionaldoxime *O*-isopropyl ether, was more active than methoprene, the most active of the JH mimics known so far, and the activity rise was 10^4 times in all, to count up from the starting terpenoid oxime *O*-ethers. Analysis of the quantitative structure–activity relationship of both the acetaldoxime and propionaldoxime series of compounds gave explanations for these findings.

Analogues of insect juvenile hormones, JH mimics, have long been candidates as insect control agents, and searches for such compounds with high activity, high field stability, and safety have been extensive. A deeper understanding of the mode of action of JH and their mimics and information concerning the topology of the receptor site may assist us in designing new active structures. With this aim, we have analyzed quantitatively the structure–activity relationship of the terpenoid, 2,4-dodecadienoate type of JH mimics (Nakayama et al., 1984). On the basis of these results, new classes of terpenoid JH mimics, undecen-2-one oxime *O*-ethers and undecen-2-yl carbamates, have been developed (Nakayama et al., 1985). The activity of these terpenoid compounds is comparable to that of the natural JH I against *Culex pipiens* (common mosquito) and *Chilo suppressaslis* (rice stem borer) and much higher against *Musca domestica* (housefly). The compounds were much less potent than methoprene [isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate], the most active of the JH-mimetic compounds known so far. Thus, to obtain higher activity, we have transformed the terpenoid structure to a nonterpenoid one, developing (4-phenoxyphenoxy)- and (4-benzylphenoxy)acetaldoxime *O*-propyl ethers (Nakayama et al., 1985) (Figure 1). The activity examined for *C. pipiens* was excellent, about 100 times that of the parent terpenoid oximes.

In this study, we first prepared a series of acetaldoxime *O*-ethers that have various substituents at both ends. The introduction of a methyl group to the meta position of the terminal benzene and to the ether end as a branch increased the activity against *C. pipiens* several times. Next, we explored more active skeletal structures and developed 3-(4-phenoxyphenoxy)- and 3-(4-benzylphenoxy)propionaldoxime *O*-ethers, the activity of which was dozens of times that of the corresponding acetaldoximes. By optimization of the terminal structures, we finally obtained 3-[4-(3-methylphenoxy)phenoxy]propionaldoxime *O*-isopropyl ether, the most potent member of the class. The activity for *C. pipiens* was higher than that of methoprene, and the increase in potency was 10^4 times in all, when counted from the starting terpenoid oxime *O*-ethers. The quantitative structure–activity relationship of both the acetaldoxime and propionaldoxime series of compounds was analyzed to help us understand the reasons for these changes in activity.

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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-Phenoxyphenols. A 9-mL portion of concentrated HCl (100 mmol) was added to pyridine (8.4 g, 100 mmol) in an ice bath. Water was removed under reduced pressure, and the residual semisolid was heated at 150 °C to remove water completely. An appropriate phenoxyanisole (9 mmol) was added to the solid heated to 120 °C, and the mixture was stirred for 40 min at 200–220 °C. After being cooled to room temperature, the mixture was dissolved in water and then extracted with ether. The ether layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure, giving an oily product.

(4-Hydroxyphenoxy)acetaldehyde Diethyl Acetal. Hydroquinone (7.3 g, 67 mmol) was added to a EtONa solution prepared by sodium metal (1.5 g, 67 mmol) being dissolved in ethanol (40 mL). The mixture was stirred for 2 days at refluxing temperature, poured into water, and treated with ether. The ether layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness. The residual oil was put on a silica gel column that was treated with 10% ethyl acetate in benzene, giving 5.90 g (39%) of the acetal: ^{1}H NMR (ppm/$CDCl_3$) 1.15 (t, 6 H, J = 7 Hz, CH_3), 3.60 (q, 4 H, J = 7 Hz, OCH_2CH_3), 3.90 (d, 2 H, J = 5 Hz, OCH_2CH), 4.77 (t, 1 H, J = 5 Hz, $CH(OEt)_2$), 5.90 (br, 4 H, C_6H_4).

(4-Bromophenoxy)acetaldehyde Diethyl Acetal. A mixture of 4-bromophenol (25 g, 150 mmol), NaOH (5.8 g, 150 mmol), and bromoacetaldehyde diethyl acetal (27 g, 140 mmol) was stirred for 2 days at 170 °C. The reaction mixture was poured into water and treated with ether. The ether layer was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness, yielding an oily product, 36 g (87%).

(4-Phenoxyphenoxy)- and (4-Benzylphenoxy)acetaldehyde Diethyl Acetals. *A. From 4-Phenoxy- and 4-Benzylphenols.* An appropriate phenol (20 mmol) and bromoacetaldehyde diethyl acetal (4.3 g, 22 mmol) were added to an ethanol solution (20 mL) in which sodium metal (0.5 g, 22 mmol) had been dissolved. The reaction mixture was stirred for 2 days at refluxing temperature, poured into ice water, and treated with benzene. The benzene layer was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness, giving an oily product.

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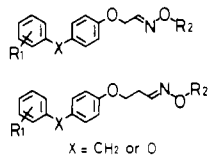


Figure 1. Structures of (4-phenoxyphenoxy)- and (4-benzylphenoxy)alkanaldoxime *O*-ethers.

B. From (4-Hydroxyphenoxy)acetaldehyde Diethyl Acetal. A mixture of (4-hydroxyphenoxy)acetaldehyde diethyl acetal (2.7 g, 10 mmol), an appropriate bromobenzene (8 mmol), KOH (0.5 g, 9 mmol, 85% purity), and a catalytic amount of copper powder was heated at 150–160 °C for 5 days. After the mixture was cooled, ether was added and the insoluble material was filtered off. The filtrate was washed with water, 2 N NaOH, and water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness, giving an oily product.

C. From (4-Bromophenoxy)acetaldehyde Diethyl Acetal. A mixture of (4-bromophenoxy)acetaldehyde diethyl acetal (3.5 g, 12 mmol), an appropriate phenol (17 mmol), K_2CO_3 (2.3 g, 17 mmol), and a catalytic amount of $CuCl_2$ was stirred for 2 days at 170 °C. After being cooled to room temperature, the mixture was poured into ether and filtered. The filtrate was washed with water, 2 N NaOH, and water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness, yielding an oily product.

3-(4-Phenoxyphenoxy)- and 3-(4-Benzylphenoxy)-propionaldehyde Diethyl Acetals. 3-Chloropropionaldehyde diethyl acetal (0.8 g, 5 mmol) and a catalytic amount of KI were added to a DMSO solution (20 mL) of an appropriate phenol (5.5 mmol) and powdered KOH (0.6 g, 11 mmol, 85% purity). After being stirred for 2 h at 70 °C, the mixture was diluted with water and extracted with benzene. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness. The residual oil was purified by silica gel column chromatography with 2–5% ethyl acetate in benzene as solvent.

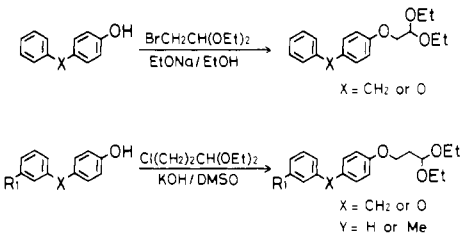
ω-(4-Phenoxyphenoxy)- and ω-(4-Benzylphenoxy)-alkanal Oxime *O*-Ethers. An aqueous solution (5 mL) of O-substituted hydroxylammonium chloride (5 mmol) and 2 N HCl (0.5 mL) was added to an appropriate diethyl acetal (3 mmol) in ethanol (20 mL). The reaction mixture was stirred for 3 h at 60 °C, diluted with water, and extracted with benzene. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness. The crude product was put on a silica gel column that was eluted with benzene–hexane, giving a pure substance.

4-Phenoxybenzaldehyde (*E*)-Oxime *O*-Ethers. An aqueous solution (5 mL) of O-substituted hydroxylammonium chloride (5 mmol) was added to an ethanol solution of 4-phenoxybenzaldehyde (0.7 g, 3.5 mmol). The mixture was stirred for 30 min at 60 °C, poured into ice water, and treated with benzene. The benzene layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to dryness, producing an oily residue. The residue was purified by silica gel column chromatography with 30% benzene in hexane as solvent.

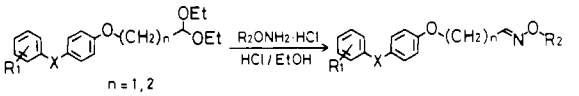
All of the previously unknown compounds were identified by elemental analysis for C, H, and N within the error of ±0.3%. This information is available as supplementary Tables I and II.

Bioassay Procedure. Forth larval instars of mosquito (*C. pipiens pallens* Coquillet) were selected from colonies maintained at 28 °C in water containing a feed mixture

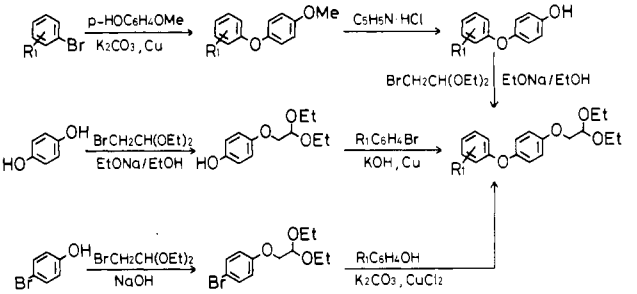
Scheme I



Scheme II



Scheme III

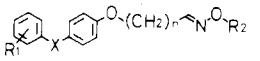


of mouse food and dry yeast. The eggs were a gift of the Sumitomo Chemical Co., Ltd. Three batch of 20 larvae each were transferred to disposable plastic tumblers containing 100 mL of water. An ethanol solution of the test compounds then was added to the tumblers (10 μL/100 mL of water), after which 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, results were scored as the percentage of unemerged adults, including those that could escape only partially from pupal cuticles. The nonemergence percentage of the control (no chemicals added except 10 μL/100 mL of ethanol) was less than 10%.

RESULTS AND DISCUSSION

Synthesis of Compounds. Commercially available 4-phenoxy- and 4-benzylphenols were reacted with bromoacetaldehyde diethyl acetal and 3-chloropropionaldehyde diethyl acetal, giving the corresponding alkanal diethyl acetals (Scheme I). These were treated with O-substituted hydroxylammonium chlorides (Nakayama et al., 1985) under acidic conditions to obtain oxime *O*-ethers **1–23** (Scheme II). For the preparation of compounds **29, 32, 33, 36, 41,** and **42,** appropriately substituted bromobenzenes were reacted with 4-hydroxyanisole in the presence of K_2CO_3 and copper. The phenoxyanisoles obtained were heated with pyridine hydrochloride to obtain the corresponding phenols, which were then converted to the final oxime *O*-ethers via diethyl acetals. Stoichimometric reactions between hydroquinone and bromoacetaldehyde diethyl acetal gave (4-hydroxyphenoxy)acetaldehyde diethyl acetal. This compound was then reacted with appropriately substituted bromobenzenes under alkaline conditions and in the presence of copper catalyst, giving acetals for the preparation of compounds **28** and **34.** (4-Bromophenoxy)acetaldehyde diethyl acetal obtained from 4-bromophenol was reacted with substituted phenols, and the products were converted to oxime *O*-ethers **24–27, 30, 31, 35, 37–40,** and **43–48.** The reaction pathways are summarized in Schemes II and III. In the syntheses, both *E* and *Z* oximes were produced; the ratio was estimated to be about 1:1 from ^1H NMR examination (Nakayama et

Table I. JH Activity and Physicochemical Properties of (4-Phenoxyphenoxy)- and (4-Benzylphenoxy)alkanal Oxime *O*-Ethers



					pI_{50}, M			physicochemical parameters							
no.	R_1	R_2	X	*n*	obsd	calcd[a]	ΔpI_{50}	D_1	D_2	D	W_1	W_1^o	T_2	I_p	log *P*
1	H	Et	CH_2	1	7.09	7.49	−0.40	6.79	4.27	11.06	6.23	1.00	3.80	0.00	4.22
2	H	Pr	CH_2	1	7.97	7.56	0.41	6.79	5.55	12.34	6.23	1.00	3.80	0.00	4.76
3	H	*i*-Pr	CH_2	1	7.72	8.04	−0.31	6.79	4.27	11.06	6.23	1.00	5.05	0.00	4.63
4	H	Allyl	CH_2	1	8.14	7.57	0.57	6.79	5.52	12.31	6.23	1.00	3.80	0.00	4.21
5	H	propargyl	CH_2	1	7.46	7.58	−0.12	6.79	5.27	12.06	6.23	1.00	3.80	0.00	3.34
6	H	Bu	CH_2	1	7.41	7.25	0.16	6.79	6.78	13.57	6.23	1.00	3.80	0.00	5.30
7	H	*i*-Bu	CH_2	1	8.48	8.11	0.37	6.79	5.55	12.34	6.23	1.00	5.05	0.00	5.17
8	H	*s*-Bu	CH_2	1	7.42	8.11	−0.67	6.79	5.55	12.34	6.23	1.00	5.05	0.00	5.17
9	H	pentyl	CH_2	1	6.72	6.55	0.17	6.79	8.05	14.84	6.23	1.00	3.80	0.00	5.84
10	H	*i*-pentyl	CH_2	1	8.10	7.80	0.30	6.79	6.78	13.57	6.23	1.00	5.05	0.00	5.71
11	H	c-pentyl	CH_2	1	8.10	7.56	0.52	6.79	5.17	11.96	6.23	1.00	5.95	0.00	5.43
12	H	c-hexyl	CH_2	1	8.12	8.11	0.01	6.79	5.55	12.34	6.23	1.00	5.05	0.00	5.87
13	H	benzyl	CH_2	1	6.75	6.98	−0.23	6.79	6.65	13.44	6.23	1.00	6.23	0.00	5.32
14	H	Et	CH_2	2	8.76	8.87	−0.11	6.79	5.48	12.27	6.23	1.00	3.80	1.00	4.76
15	H	Pr	CH_2	2	8.37	8.58	−0.21	6.79	6.71	13.50	6.23	1.00	3.80	1.00	5.30
16	H	*i*-Pr	CH_2	2	9.68	9.41	0.27	6.79	5.48	12.27	6.23	1.00	5.05	1.00	5.17
17	H	c-pentyl	CH_2	2	8.42	8.41	−0.32	6.79	6.40	13.19	6.23	1.00	5.90	1.00	4.66
18	H	H	O	2	6.58	6.50	0.08	6.62	2.98	9.60	6.23	1.00	2.70	1.00	3.63
19	H	Et	O	2	9.09	8.88	0.21	6.62	5.48	12.10	6.23	1.00	3.80	1.00	4.95
20	H	*i*-Pr	O	2	9.76	9.42	0.34	6.62	5.48	12.10	6.23	1.00	5.05	1.00	5.36
21	3-Me	Et	O	2	9.46	9.60	−0.14	7.73	5.48	13.21	7.18	1.00	3.80	1.00	5.51
22	3-Me	*i*-Pr	O	2	10.00	10.14	−0.15	7.73	5.48	13.21	7.18	1.00	5.05	1.00	5.92
23	H	Pr	O	1	7.54	7.56	−0.04	6.62	5.55	12.17	6.23	1.00	3.80	0.00	4.95
24	2-Me	Pr	O	1	7.36	7.50	−0.14	6.62	5.55	12.17	7.44	1.52	3.80	0.00	5.47
25	2-MeO	Pr	O	1	6.81	6.65	0.16	6.67	5.55	12.22	8.55	1.35	3.80	0.00	4.87
26	2-F	Pr	O	1	7.35	7.61	−0.26	6.62	5.55	12.17	6.78	1.35	3.80	0.00	5.16
27	2-Cl	Pr	O	1	6.89	6.91	−0.02	6.62	5.55	12.17	7.60	1.80	3.80	0.00	5.71
28	$2\text{-}CF_3$	Pr	O	1	6.18	6.30	−0.12	6.62	5.55	12.17	7.97	1.98	3.80	0.00	5.94
29	3-Me	Pr	O	1	8.71	8.28	0.43	7.73	5.55	13.28	7.18	1.00	3.80	0.00	5.48
30	3-Et	Pr	O	1	7.85	7.65	0.20	9.04	5.55	14.59	7.27	1.00	3.80	0.00	5.91
31	3-MeO	Pr	O	1	7.41	7.74	−0.33	8.80	5.55	14.43	7.22	1.00	3.80	0.00	4.93
32	3-F	Pr	O	1	8.27	8.21	0.06	7.19	5.55	12.74	6.78	1.00	3.80	0.00	5.21
33	3-Cl	Pr	O	1	8.12	8.12	0.00	8.04	5.55	13.59	7.60	1.00	3.80	0.00	5.74
34	$3\text{-}CF_3$	Pr	O	1	7.47	8.01	−0.54	8.23	5.55	13.78	7.66	1.00	3.80	0.00	5.93
35	$3\text{-}NO_2$	Pr	O	1	7.75	7.69	0.06	8.31	5.55	13.86	8.01	1.00	3.80	0.00	4.95
36	4-Me	Pr	O	1	6.84	7.44	−0.60	7.48	5.55	13.03	6.23	1.00	3.80	0.00	5.47
37	4-Et	Pr	O	1	6.42	6.92	−0.50	8.70	5.55	14.25	6.23	1.00	3.80	0.00	5.89
38	4-Pr	Pr	O	1	6.36	6.52	−0.16	9.99	5.55	15.54	6.60	1.00	3.80	0.00	6.38
39	4-MeO	Pr	O	1	7.34	7.02	0.32	8.53	5.55	14.08	6.23	1.00	3.80	0.00	4.87
40	4-EtO	Pr	O	1	6.86	6.51	0.35	9.81	5.55	15.36	6.47	1.00	3.80	0.00	5.25
41	4-F	Pr	O	1	7.58	7.57	0.01	6.73	5.55	12.28	6.23	1.00	3.80	0.00	5.16
42	4-Cl	Pr	O	1	7.26	7.43	−0.17	7.50	5.55	13.05	6.23	1.00	3.80	0.00	5.71
43	$4\text{-}NO_2$	Pr	O	1	7.08	7.25	−0.17	8.04	5.55	13.59	6.23	1.00	3.80	0.00	4.98
44	$2,3\text{-}Me_2$	Pr	O	1	7.90	7.28	0.62	7.73	5.55	13.28	7.44	1.52	3.80	0.00	5.97
45	$2,5\text{-}Me_2$	Pr	O	1	6.61	6.38	0.23	7.73	5.55	13.28	8.40	1.52	3.80	0.00	5.97
46	$3,5\text{-}Me_2$	Pr	O	1	7.98	7.77	0.21	7.73	5.55	13.28	8.14	1.00	3.80	0.00	5.98
47	$2,3,5\text{-}Me_3$	Pr	O	1	6.22	6.21	−0.16	7.73	5.55	13.28	8.40	1.52	3.80	0.00	6.45
48	$2,3,6\text{-}Me_3$	Pr	O	1	5.68	5.89	−0.21	7.73	5.55	13.28	8.66	1.52	3.80	0.00	6.46

[a] Values were calculated with eq 4.

al., 1985). The oxime could not be separated by conventional chromatographic technique, and thus the compounds listed in Table I were bioassayed as mixtures of both isomers.

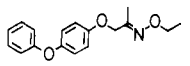
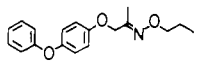
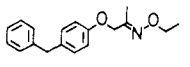
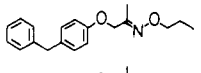
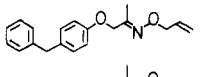
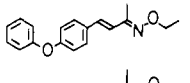
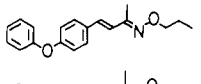
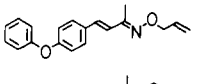
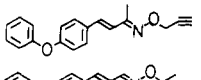
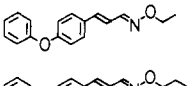
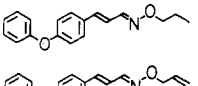
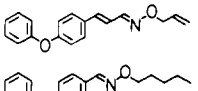
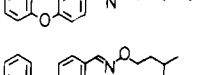
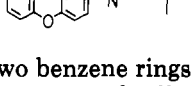
Acetone (*E*)-oxime *O*-ethers **49–51** and **53** were prepared by the same method as reported (Nakayama et al., 1985) for compound **52**. 3-Buten-2-one (*E*)-oxime *O*-ethers **54**, **56**, and **57** were prepared by the method described for the synthesis of compound **55**, and cinnamaldehyde (*E*)-oxime *O*-ethers **58** and **60**, by the method for compound **59** (Nakayama et al., 1985). Benzaldehyde (*E*)-oxime *O*-ethers **61** and **62** were prepared by the reaction of 4-phenoxybenzaldehyde with an appropriate O-substituted hydroxylammonium chloride. These compounds are listed in Table II.

JH Activity of Acetaldoxime *O*-Ethers. Bioassay was made with a synchronized sensitive stage of *C. pipiens*. The activity was expressed in terms of pI_{50} (M), the logarithm of the reciprocal of the concentration at which 50% inhibition of metamorphosis is observed. The data are summarized in Table I.

In the (4-benzylphenoxy)acetaldehyde oxime series of compounds **1–13**, where the structure of the ether moiety (R_2) was systematically altered, propyl compound **2** and those having alkyls of a similar length, allyl **4** and propargyl **5**, had higher activities than those with shorter or longer alkyls. In addition, bulkiness due to branching or cyclization, if appropriate, appeared to raise the activity further, the most active member of this subclass, isobutyl **7**, fulfilling both conditions.

The effect of substitution on the benzene ring at another end (R_1) was examined by preparation of the phenoxyphenoxy type of compounds **23–48**, where the ether end was fixed to *n*-propoxy. The exchange of the connecting

Table II. Analogues of the Alkanaldoxime *O*-Ethers and Their JH Activity

no.	structure	pI_{50}
49		7.30
50		7.53
51		6.99
52		7.02
53		7.14
54		6.58
55		6.28
56		6.33
57		6.72
58		6.76
59		6.59
60		6.38
61		5.46
62		6.26

link between the two benzene rings from a methylene to an oxygen atom does not much affect activity (Nakayama et al., 1985). Introduction of substituents at the ortho or para position, or both, lowered activity, whereas meta-substituted compounds had activity higher than or comparable to that of the unsubstituted compound **23**. The set of substituents at each position was chosen so that we could examine the steric, hydrophobic, and electric effects. That 3-methyl derivative **29** had the highest activity in the subclass suggests that there is an optimum steric condition, because the bulkier ethyl (**30**), methoxy (**31**), and trifluoromethyl (**34**) and smaller fluoro (**32**) and unsubstituted (**23**) compounds were less active. On the basis of the whole molecule, the total length in the fully extended conformation of this and other active compounds corresponds to the optimum one, about 21 Å, suggested by our previous structure–activity relationship studies (Nakayama et al., 1984, 1985).

Development of Propionaldoxime *O*-Ethers. The potency of the most active compounds (**29**) in the acetaldoxime *O*-ether series may be raised by introduction of a branch or a cyclic structure into the ether moiety. Before this was done, however, we searched for a better skeletal structure that would confer higher activity. The modification made by simple alteration of the ethylene bridge between the phenoxyphenoxy and oxime moieties to a longer one was fruitful. The propionaldoxime *O*-ethers thus obtained had activities dozens of times greater than that of the acetaldoximes *O*-ethers with the corresponding total length, e.g. ethyl **19** and propyl **23**. On the basis of structure vs. activity information obtained for the acetaldoxime, we optimized the structure in the 3-(4-phenoxyphenoxy)propionaldoxime series by introduction of a branch into the ether moiety and by 3-metylation of the terminal benzene to obtain compound **22**. The effect on *C. pipiens* only was investigated. The activity of this compound exceeded that of methoprene, the most potent of the JH-mimetic compounds known so far.

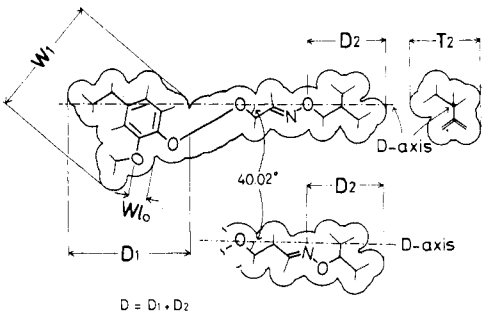


Figure 2. Schematic representation of the steric parameters. The ends of the bars of the structure represent hydrogen atoms.

Other structures examined are listed in Table II, together with their activity against *C. pipiens*. The acetone oxime *O*-ethers **49–53** had activity similar to or somewhat less than that of the corresponding acetaldoxime *O*-ethers. The methyl branch at the oxime carbon atom may sterically disturb the interaction of the molecule with the receptor or obstruct the taking on of the conformation needed for the fit to the receptor. The activities of 4-(4-phenoxyphenyl)-3-buten-2-one oxime *O*-ethers **54–57**, 4-phenoxycinnamaldehyde oxime *O*-ethers **58–60**, and 4-phenoxybenzaldehyde oxime *O*-ethers **61** and **62** are 10–100 times less active than the corresponding acetaldehyde oxime *O*-ethers with a similar chain length. A common structural peculiarity of these compounds is the ene or diene structure conjugated with the benzene ring. This structure may reduce their conformational flexibility for fitting to the receptor.

Quantitative Structure–Activity Relationship. Quantiative analysis was done of the acetaldoxime and propionaldoxime series of compounds listed in Table I. Our immediate aim was to understand the rise in activity. Another point of interest was to understand the steric conditions that confer activity in compounds with different skeletal structures, i.e. this set of compounds and those reported previously (Nakayama et al., 1984, 1985).

Steric Parameters. To express the steric features of the molecule, we first defined the *D*-axis that passes through the alkoxy oxygen atom and the oxygen atom β to the oxime carbon atom in the fully extended conformation of the acetaldoxime *O*-ethers. By this definition, the angle between the *D*-axis and the bond that connects the β-oxygen atom to the oxime moiety is 40.02°. For the propionaldoxime *O*-ethers, the *D*-axis was drawn so as to pass on the oxygen atom β to the oxime carbon, and satisfying this angle condition (Figure 2). In the extended conformation, the terminal benzene ring was placed flat on the same plane as that of the zigzag alkanaldoxime chain. The central benzene ring can fully rotate, without affecting the values of the dimensional parameters defined below. In Figure 2, to show the definition, the molecule is drawn so that the angle between the two benzene rings becomes 90°. At this angle, the mutual overlap of the van der Waals radii becomes least significant between ortho substituents in both the phenoxyphenoxy and benzylphenoxy types of compounds. Recent molecular orbital calculations have shown that the two benzene rings are perpendicular to each other in the lowest energy conformation (Nakayama and Richard, 1987).

On the basis of the conformation defined above, the lengths along the *D*-axis of the two ends, D_1 and D_2, were

defined. D_1 is the length along the D-axis of the terminal benzyl and phenoxy moieties. The length of the alkoxy end, D_2, is that from the connecting oxygen atom for the acetaldoxime series of compounds. The D_2 of the propionaldoximes is measured from the point on the D-axis that corresponds to the alkoxy oxyen atom of the acetaldoximes, when the terminal benzene moiety overlaps that of the acetaldoximes. So it is essentially the length from the oxime nitrogen atom to the ether end. Since the length of the rest of the molecule from which D_1 and D_2 are subtracted is constant, the sum of D_1 and D_2 corresponds to the total length of the molecule and is expressed as D. The D parameters have been originally devised for analysis of the 2,4-dodecadienoate series of JH mimics (Nakayama et al., 1984). The definition in this study was thus made in consideration of the correspondence between the present and previous series of compounds in terms of D.

To express the steric dimensions of the two terminal moieties in more detail, we further defined the following steric parameters. W_1 is the width of the benzene end in the direction perpendicular to its connecting axis to the rest of the molecule. $W_1°$ is the width of the left-hand site of the ortho substituents when viewed from the connecting end and the longest chain of the substituents is placed to the right; in other words, it is the width in the direction opposite to the one in which the main chain extends and thus corresponds to the minimum width of the substituents. T_2 is the thickness of the alkoxy moiety in vertical direction to the zigzag, backbone plane. The situations are summarized in Figure 2. These parameters of length and width are expressed in angstroms and listed in Table I. Steric dimensions other than these, such as the thickness of the D_1 moiety, width of the D_2 moiety, etc., were also considered in the analysis. They were, however, not significant at all for this set of compounds and thus are not indicated in the figure. The steric parameters were calculated based on the CPK model with a computer program devised for the estimation of the D and related dimensional parameters (Asao and Iwamura, unpublished results).

Hydrophobicity. The hydrophobicity of the molecule was expressed by the logarithm of the partition coefficient between 1-octanol/water, log P. The method of estimation was essentially the same as that used in our earlier studies of 2,4-dodecadienoate derivatives (Nakayama et al., 1984) and undecen-2-one oxime O-ethers and undecen-2-yl carbamates (Nakayama et al., 1985). The π values used specific for the present series of compounds were estimated as follows: π[4-(PhCH$_2$)PhO](3.15) = π(PhO)(1.14) + $\pi_{PhCH_2}^{benzene}$(2.01) and π[4-(PhO)PhO-](3.22) = π(PhO) + $\pi_{PhO}^{benzene}$. For the π(PhO) vlaue, we adopted the mean (1.14) of two calculations: log P(PhCH$_2$OPh) (3.79) − log P(PhCH$_3$) (1.10) and log P(CH$_2$CH=CH$_2$OPh) (2.94) − log P(CH$_2$CH=CH$_3$) (1.77). The values for alkyl moieties were calculated by consecutive addition of the π(CH$_3$) value (0.54), and when necessary, the fragment factors for a chain branch, F_{cBr} (−0.13), a double bond, $F_=$ (−0.55), and a triple bond, $F_\equiv$ (−1.42), were also considered. The data used for these calculations were taken from the literature (Hansch and Leo, 1979).

The log P values of the compounds with aromatic substituents on the terminal benzene ring were calculated by addition of the π values of the substituents to the corresponding unsubstituted compounds. The aromatic π values adopted were those for anisole compounds and were calculated by the equation formulated in consideration of the bidirectional electronic effect (Fujita, 1983).

π_X of MeOPh–X = 0.924 $\pi_X^{benzene}$ + 0.272σ_X − 0.193ρ_X-(para) + 0.037. ρ_X is the constant for X with H-bonding ability and represents the extent of the effect exerted by the OMe substituent on the solvation and thus on the hydrophobicity.

In the analyses, these log P values were not significant for this set of compounds but are listed in Table I for comparison with data in earlier papers (Nakayama et al., 1984, 1985).

Analysis. First we analyzed the compounds (**1–20, 23**) with various alkyls at the ether end but a fixed, unsubstituted benzene at another terminal. Of the various combinations of the parameters described above as independent variables, eq 1 gave the best correlation. In this

$$pI_{50} = \underset{(1.51)}{1.69D_2} - \underset{(0.13)}{0.16D_2^2} + \underset{(2.25)}{4.42T_2} - \underset{(0.27)}{0.46T_2^2} + \underset{(0.39)}{1.27I_p} - \underset{(4.32)}{7.05} \quad (1)$$

$$n = 21,\ s = 0.37,\ r = 0.93,\ F_{5,15} = 19.24$$

and the following equations, 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. Both the D_2 and T_2 parameters are significant together with their squared terms, indicating that there are optimum steric conditions in terms of length and thickness. I_p is the indicator variable that is 1 for the propionaldoxime series of compounds and 0 for acetaldoximes. The number of the propionaldoximes, 9, is sufficiently great for placing confidence in the significance of the I_p term in the correlation (Topliss and Costello, 1972). Its positive coefficiant, about 1.3, suggests that the activity is about 20 times higher in the former series than in the latter.

For the acetaldoxime series of compounds (**2, 23–48**) with a fixed R_2 (n-propyl) but various aromatic substituents at the terminal benzene, eq 2 was obtained. The D_1

$$pI_{50} = \underset{(0.17)}{-0.44D_1} + \underset{(3.68)}{12.22W_1} - \underset{(0.25)}{0.82W_1^2} - \underset{(0.66)}{2.22W_1°} + \underset{(13.06)}{31.30} \quad (2)$$

$$n = 27,\ s = 0.34,\ r = 0.90,\ F_{4,22} = 23.84$$

was significant with a negative sign, but its squared terms was not. This suggests that the length along the D-axis of this O-propyl ether set of compounds are supraoptimum. An optimum condition exists, however, for the whole width (W_1). The negative coefficient of the $W_1°$ term suggests that the wider the ortho substituents in the W_1 direction, and weaker the activity.

To see the structure–activity relationship on the basis of the whole molecule, both equations were combined, including compounds **21** and **22** (eq 3).

$$pI_{50} = \underset{(0.15)}{-0.45D_1} + \underset{(3.31)}{11.98W_1} - \underset{(0.23)}{0.81W_1^2} - \underset{(0.64)}{2.24W_1°} + \underset{(1.19)}{1.50D_2} - \underset{(0.10)}{0.14D_2^2} + \underset{(0.27)}{4.64T_2} - \underset{(0.22)}{0.48T_2^2} + \underset{(0.28)}{1.27I_p} - \underset{(11.78)}{45.01} \quad (3)$$

$$n = 48,\ s = 0.34,\ r = 0.95,\ F_{9,38} = 37.68$$

Since the D_1 and D_2 are the lengths along the common D-axis, we reformed eq 3 by using the $D_1 + D_2$ term, i.e. D, to obtain eq 4.

$$pI_{50} = \underset{(1.62)}{2.91D} - \underset{(0.06)}{0.12D^2} + \underset{(3.17)}{11.47W_1} - \underset{(0.22)}{0.78W_1^2} - \underset{(0.59)}{1.92W_1°} + \underset{(1.94)}{4.67T_2} - \underset{(0.21)}{0.48T_2^2} + \underset{(0.28)}{1.30I_p} - \underset{(14.20)}{59.81} \quad (4)$$

$$n = 48,\ s = 0.34,\ r = 0.95,\ F_{8,39} = 43.14$$

The optimum for D was calculated to be about 12. The D values of almost all of the acetaldoxime O-propyl ethers

Table III. Development of Equation 4

const	D^2	D	W^2	W	T^2	T	$W_1°$	I_p	s	r	$F_{X,Y}$[a]
7.37								1.53	0.77	0.62	$F_{1,46}$ = 29.11
−7.47					−0.65	6.34		1.62	0.62	0.78	$F_{2,44}$ = 12.92
−40.19			−0.67	9.53	−0.61	6.03		1.53	0.53	0.86	$F_{2,42}$ = 9.14
−38.63			−0.64	9.37	−0.60	5.90	−1.34	1.46	0.47	0.89	$F_{1,41}$ = 12.18
−59.81	−0.12	2.91	−0.78	11.47	−0.48	4.70	−1.92	1.30	0.34	0.95	$F_{2,39}$ = 20.30

[a] F statistic for the significance of the addition of each variable.

Table IV. Squared Correlation Matrix for Variables Used in Equation 4

	D	W	T	$W_1°$
W	0.03			
T	0.00	0.09		
$W_1°$	0.02	0.42	0.04	
I_p	0.06	0.05	0.02	0.05

of eq 2 exceed this figure, which makes the negative coefficient of the D_1 term reasonable. The developments of this final eq 4 and the squared correlation matrix for the variables considered are shown in Tables III and IV, respectively.

Discussion and Prospects. On the basis of the optimum D (12.1 Å) calculated from the correlation eq 4, the optimum total length was estimated to be about 21 Å. In our previous work on the 2,4-dodecadienoate series of JH mimics, the optimum size for activity against *Aedes aegypti* and *Tenebrio molitor* was calculated to be about 21 Å. That the figures are the same suggests that this optimum length of molecule is common to a variety of active compounds and for a variety of insect species. The existence of a suitable length for JH activity has been postulated (Henrick, 1982; Nilles et al., 1977), but not fully quantitated. Throughout the analyses, the hydrophobicity of the molecule was not introduced as a significant variable over the 90% level. This seems to be due to the narrower range of variation of the log P values in this set of compounds, and the dependency of the JH activity on it is probably weaker than on the steric nature (Nakayama et al., 1984).

The negative coefficient of $W_1°$ term explains the activity of ortho-substituted compounds being lower than the corresponding unsubstituted ones. The W_1 parameter corresponds to the minimum width of the substituents. Its significance at the ortho position with a negative sign may show intramolecular interference with the connecting X moiety (oxygen, methylene) or some other part of the molecule, which obstructs taking on of the best conformation for the fit to the receptor. No particular steric parameters are significant for meta and para positions in eq 4, but the width W_1 of the compounds with a meta substituent bulkier than methyl exceeds the optimum value, 7.4 Å. Similarly, the D values for most of the para-substituted compounds exceeded the optimum. For the ether moiety, the optimum width in terms of T_2, 4.9 Å, is just satisfied by a methyl branch.

The steric parameters were defined on the conformation shown in Figure 2, where the terminal benzene was flat on the plane of the page with the central benzene perpendicular to it. Both rings could, however, be twisted within a certain range so that the D values do not vary enough, and the actual conformation at the site of action is probably in this range. The D values defined on a different conformation would not explain the variation of the activity effectively; in other words, the correlation equation like eq 4 could not be formulated with the set of the D values significantly different from the present one. On the basis of similar reasons, we postulated the "active conformation" of the terpenoid JH mimics to be a rather extended one (Nakayama et al., 1984). In relation to this result, the conformational correspondence of the (4-phenoxyphenoxy)acetaldoxime *O*-ethers and terpenoid methoprene has been examined by means of molecular orbital calculations and computer graphics (Nakayama and Richard, 1987). The results suggested that (4-phenoxyphenoxy)acetaldoxime *O*-ethers are superimposable on methoprene, with the two benzene rings twisted rectangularly to each other and the side chain moiety 60–120° from the plane of the attached benzene.

The activity of a propionaldoxime is higher than that of the corresponding acetaldoxime. The reason is not known, but a position-specific electronic or hydrophobic interaction is one possibility; the oxime moiety may come to the interaction site of the receptor more suitably when built in the propionaldoxime structure within the framework indicated by the optimum molecular length, about 21 Å.

The most potent compound, **22**, in this set of compounds satisfies most conditions for high activity. The total length along the D-axis of the compound somewhat exceeds the optimum value. The exchange of the isopropyl at the ether end to a methyl shorter by one methylene unit gives the D closest to the optimum, but the favorable branch effect is lost. Elimination of the *m*-methyl gives compound **20**, whose activity is somewhat lower. The D value of this compound is closer to the optimum, but the W_1 value is smaller than its optimum.

Based on eq 4, within this skeletal class, a number of compounds can be expected to have activity as high as that of **22** or at least methoprene, and their synthesis are under consideration. More important is the extension of the results of other classes of compounds. We have estimated the structural parameters of highly active propionaldoxime *O*-2-(4-phenoxyphenoxy)ethyl ether (Ohsumi et al., 1985) in which the oxime moiety is built in the structure in the reverse of the present series of compounds, and we predicated the pI_{50} value by eq 4 to be 9.00. The activity tested in our laboratory of the compound provided by the Sumitomo Chemical Co., Ltd., was 9.50, which agreed with the prediction. The structural information obtained through this work and that reported previously (Nakayama et al., 1984, 1985) may be helpful in the design or exploration of new active structures.

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Registry No. **1**, 101322-66-1; **2**, 101322-67-2; **3**, 112597-65-6; **4**, 101322-68-3; **5**, 112597-66-7; **6**, 112597-67-8; **7**, 112597-68-9; **8**, 112597-69-0; **9**, 112597-70-3; **10**, 112597-71-4; **11**, 112597-72-5; **12**, 112597-73-6; **13**, 112597-74-7; **14**, 112597-75-8; **15**, 112597-76-9; **16**, 112597-77-0; **17**, 112597-78-1; **18**, 98116-79-1; **19**, 98116-74-6; **20**, 112597-79-2; **21**, 112597-80-5; **22**, 112597-81-6; **23**, 98116-77-9; **24**, 112597-82-7; **25**, 112597-83-8; **26**, 112597-84-9; **27**, 112597-85-0; **28**, 112597-86-1; **29**, 112597-87-2; **30**, 112597-88-3; **31**, 112597-89-4; **32**, 112597-90-7; **33**, 112597-91-8; **34**, 112597-92-9; **35**, 112597-93-0; **36**, 112597-94-1; **37**, 112597-95-2; **38**, 112597-96-3; **39**, 112597-97-4;

40, 112597-98-5; 41, 112597-99-6; 42, 112598-00-2; 43, 112598-01-3; 44, 112598-02-4; 45, 112598-03-5; 46, 112598-04-6; 47, 112598-05-7; 48, 112598-06-8; 49, 112598-07-9; 50, 112598-08-0; 51, 112598-09-1; 52, 98901-76-9; 53, 112598-10-4; 54, 112598-11-5; 55, 98901-74-7; 56, 112598-12-6; 57, 112598-13-7; 58, 112598-14-8; 59, 98901-75-8; 60, 112598-15-9; 61, 112598-16-0; 62, 112598-17-1; (4-hydroxyphenoxy)acetaldehyde diethyl acetal, 14353-62-9; hydroquinone, 123-31-9; (4-bromophenoxy)acetaldehyde diethyl acetal, 112598-18-2; 4-bromophenol, 106-41-2; bromoacetaldehyde diethyl acetal, 2032-35-1; (4-phenoxyphenoxy)acetaldehyde diethyl acetal, 53593-05-8; (4-benzylphenoxy)acetaldehyde diethyl acetal, 98901-73-6; 3-chloropropionaldehyde diethyl acetal, 35573-93-4.

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

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Synthesis of Phenoxyaminocyclotriphosphazatrienes

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The following phosphazene compounds were synthesized for study as urease inhibitors: 2-phenoxy-2,4,4,6,6-pentaaminocyclotriphosphazatriene (**1**), *cis*-2,4-diphenoxy-2,4,6,6-tetraaminocyclotriphosphazatriene (**2**), *trans*-2,4-diphenoxy-2,4,6,6-tetraaminocyclotriphosphazatriene (**3**), *cis,trans*-2,4,6-triphenoxy-2,4,6-triaminocyclotriphosphazatriene (**4**), *cis,cis*-2,4,6-triphenoxy-2,4,6-triaminocyclotriphosphazatriene (**5**). These compounds were characterized by elemental analysis, high-performance liquid chromatography, infrared absorption spectroscopy, and nuclear magnetic resonance spectroscopy.

The enzymatic hydrolysis of urea fertilizer in the soil leads to the loss of nitrogen via ammonia volatilization; losses of up to 50% of the applied nitrogen occur in flooded soil systems such as paddy rice (Vlek and Craswell, 1981). One approach to reducing ammonia losses is the use of fertilizers that contain compounds that inhibit soil urease activity and retard urea hydrolysis. Phenoxyaminocyclotriphosphazatrienes are presently being investigated as soil urease inhibitors.

In the last three decades, significant progress has been made in several phases of phosphazene chemistry. Specifically, much research work has been focused on the chemical reactions of hexachlorocyclotriphosphazatriene ($N_3P_3Cl_6$), spectroscopic studies, molecular structure, bonding in the cyclophosphazenes, and the development of cyclic oligomers and open-chain polyphosphazenes. Several reviews have been written on phosphazene chemistry: Allcock (1972), Keat and Shaw (1973), Shaw (1975), Krishnamurthy et al. (1978), Shaw (1978).

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The six-membered ring system has been studied more intensively than any other phosphazene. X-ray crystallographic analyses of $N_3P_3F_6$ (Dougill, 1963) and $N_3P_3Cl_6$ (Wilson and Carroll, 1960) show that the rings are planar; the geometry of the cyclophosphazene ring is determind by the number, type, and arrangement of substituents (Mani et al., 1965, 1966; Shaw, 1975, 1978).

Many organophosphazenes have been synthesized by nucleophilic substitutions of hexachlorocyclotriphosphazatriene (Allcock et al., 1966; Allcock and Kugel, 1965; Allcock and Smeltz, 1976; Dell et al., 1966; Fitzsimmons and Shaw, 1964; Ford et al., 1966; Shaw, 1967). In the synthesis of phenoxy- and (*p*-bromophenoxy)-chlorocyclotriphosphazatrienes, the degrees of replacement of chlorine atoms have been determined and show that the replacement pattern is nongeminal; thus, both cis and trans isomers are formed (Dell et al., 1965, 1966).

In this paper we describe the syntheses of the following compounds: 2-phenoxy-2,4,4,6,6-pentaaminocyclotriphosphazatriene (**1**), *cis*-2,4-diphenoxy-2,4,6,6-tetraaminocyclotriphosphazatriene (**2**), *trans*-2,4-diphenoxy-2,4,6,6-tetraaminocyclotriphosphazatriene (**3**), *cis,trans*-2,4,6-triphenoxy-2,4,6-triaminocyclotriphosphazatriene (**4**), *cis,cis*-2,4,6-triphenoxy-2,4,6-triaminocyclotriphosphazatriene (**5**).

The modification of a synthetic route employed in the synthesis of triphenoxytriaminocyclotriphosphazatrienes was used in this work; the aminolysis reaction was performed in a Parr pressure reaction apparatus with use of

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