shows that the insecticidal effectiveness of the cyclodextrin formulation is at least equal to that of the standard WSC formulation. However, the formulation of Phosdrin as the β-cyclodextrin cryptate would only be attractive economically if the cost of β-cyclodextrin decreased appreciably.

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Registry No. Mevinphos, 7786-34-7; β-cyclodextrin, 7585-39-9; PCDC, 98838-08-5.

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Development of Insect Juvenile Hormone Active Oxime *O*-Ethers and Carbamates

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Results of previous quantitative structure–activity relation analyses of insect juvenile hormone active compounds prompted us to design undecen-2-one oxime *O*-ethers and undecen-2-yl carbamates. Their activities against *Culex pipiens* (common mosquito), *Chilo suppressalis* (rice stem borer), and *Musca domestica* (housefly) were comparable to that of naturally occurring JH I. To produce higher activities, we hybridized the structures of the oxime *O*-ethers and the reportedly highly active 2-(4-phenoxyphenoxy)ethyl carbamates and obtained compounds whose activities against *C. pipiens* were comparable to the 90–100% inhibition of metamorphosis by methoprene, the most highly active of the JH mimetic compounds.

The juvenile hormones (JH) have long been considered as a rational source for the design of a new regulator of insect growth. With the aim of less costly synthesis and more field stability than is possible with natural juvenile hormones, we prepared and tested a number of analogous compounds for their activities against various insect species, on the assumption that structural mimicry also mimics activity. Knowledge of what structural essentials confer the activity of an already known series of compounds should be very useful for this purpose. Quantitative structure–activity relation (QSAR) analysis also should be an efficient research tool. In recent analyses of JH activity against two insect species, *Aedes aegypti* (yellow fever mosquito) and *Tenebrio molitor* (yellow mealworm), by natural JHs and a related 2,4-dodecadienone series of compounds (Nakayama et al., 1984), we found that the steric dimensions and hydrophobicity of the molecule are important factors in the governing of JH activity.

From these results and the assumption that information on the structure vs. activity relation of one class of compounds is applicable to other types of compounds, we designed undecen-2-one oxime *O*-ether and undecen-2-yl carbamate structures. These compounds have been proved as active as JH I against *Culex pipiens* (common mosquito) and *Chilo suppressalis* (rice stem borer) and to be much more active than JH I against *Musca domestica* (housefly). Their structure–activity profiles were collated with previous QSAR results, providing further evidence of common structural features that confer JH activity throughout insect species. To obtain higher activity, we hybridized the structures of the oxime *O*-ethers and the reportedly highly active 2-(4-phenoxyphenoxy)ethyl carbamates (Karrer and Farooq, 1981) to produce (4-phenoxyphenoxy)- and (4-benzylphenoxy)acetaldehyde oxime *O*-ethers and related compounds. The activity of some of these substances on *C. pipiens*, in terms of 90–100% inhibition of metamorphosis, was as potent as, or slightly less potent than, methoprene, the most active of the JH mimetic compounds known so far.

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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 JOEL PMX-60 spectrometer. IR spectra were recorded on a Shimadzu IR-27G spectrometer.

(3*E*)-6,10-Dimethyl-3,9-undecadien-2-ol (3a). (3*E*)-6,10-Dimethyl-3,9-undecadien-2-one (**2a**; 19.4 g, 0.1 mol) was added in drops to a suspension of $LiAlH_4$ (1.9 g, 0.05 mol) in dry ether (140 mL) at −7 °C over a period of 0.5 h. After this combination was stirred for 10 min at the same temperature, ether saturated with water was added to the reaction mixture which was kept below −5 °C. The white precipitate was removed by filtration through Celite. The filtrate was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving a colorless oil. This oil was applied to a silica gel column that then was treated with 20% ethyl acetate in *n*-hexane, giving 15.0 g (77%) of **3a**: ^{1}H NMR ($CDCl_3$) δ 4.18 (m, 1, CHOH), 5.00 (br t, 1, J = 7 Hz, CH=C(CH_3)$_2$), 5.35 (m, 2, CH=CH); IR (film) 3350 (OH) cm^{-1}.

(3*E*)-6,10-Dimethyl-3-undecen-2-ol (3b). (3*E*)-6,10-Dimethyl-3-undecen-2-one (**2b**; 8.7 g, 0.044 mol) was reduced by the same procedure essentially as that described

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for **3a**, giving 7.1 g (81%) of **3b**: ^{1}H NMR (CCl_4) δ 4.10 (m, 1, CHOH), 5.40 (m, 2, CH=CH); IR (film) 3350 (OH) cm^{-1}.

Oxime *O*-Ethers 4–14. Oxime *O*-ethers **4–14** were synthesized from ketones **2a** and **2b** by adding a water solution (5 mL) of O-substituted hydroxylammonium chloride (15 mmol) to a solution of 10 mmol of ketone **2a** and **2b** in ethanol (20 mL). After 3 h of stirring at room temperature, the reaction mixture was poured into ice water and treated with *n*-hexane. The hexane extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo, which produced an oily residue. This oil was applied to a silica gel column that then was flushed with benzene–hexane, giving the *E* and *Z* oxime *O*-ethers.

Carbamates 27–38. Carbamates **27–38** were synthesized by heating a solution of an appropriate alcohol (**3a** or **3b**) (5 mmol), an appropriate isocyanate (7.5 mmol), and a few drops of triethylamine in 2 mL of dry benzene at 100 °C for 15 h in a sealed tube. The reaction mixture was diluted with benzene and then washed with water, 1 N HCl, and water. The benzene layer was dried over $MgSO_4$ and concentrated in vacuo, giving an oil. This crude oil was applied to a silica gel column that then was flushed with benzene–ethyl acetate, producing the pure substances.

Epoxides 15–20, 39–44, and 50. The method of Nilles et al. (1976) was modified slightly to obtain epoxides **15–20**, **39–44**, and **50** from the starting olefines **4–10** and **27–32**: A total of 5.5 mmol (1.36 g) of *m*-chloroperbenzoic acid (70% purity) was added slowly to a solution of 5 mmol of an olefin in dichloromethane (20 mL) at the ice bath temperature. This mixture was stirred for 1.5 h at room temperature and then shaken with 2 N Na_2CO_3. The organic layer was separated and its aqueous phase treated with dichloromethane. The combined extracts were washed with 10% $NaHSO_3$ solution followed by aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was applied to a silica gel column that then was flushed with benzene–ethyl acetate, yielding the pure substances.

Methoxides 22–24 and 45–49. The methoxy analogues **22–24** and **45–49** were prepared by methoxymercuration–demercuration of olefins **4–11** and **27–32** according to the method of Wakabayashi (1969): A solution of mercuric acetate (1.60 g, 5 mmol) in 30 mL of methanol was added slowly to a stirred, ice-cooled solution of 5 mmol of the appropriate olefin. After the mixture was stirred for 1.5 h in an ice bath, a solution of KOH (0.86 g, 15 mmol) in methanol (15 mL) was added and then $NaBH_4$ (0.10 g, 2.6 mmol). Stirring was continued for 30 min, after which the supernatant was decanted from the Hg, concentrated to a half-volume under reduced pressure, diluted with water, and treated with benzene. The benzene layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving a crude product that was applied to a silica gel column and then was flushed with benzene–ethyl acetate.

***O*-Allyl and *O*-Propargyl Oximes 21, 25, and 26.** Compounds **21**, **25**, and **26** were prepared by alkylation of their corresponding O-unsubstituted oximes **50** and **51** according to the method of Bull et al. (1980): Allyl or propargyl bromide (6.5 mmol), 5 mL of 1 N KOH, and 0.1 g of tetrabutylammonium bromide were added to a solution of the oxime (4.3 mmol) in 4 mL of dichloromethane. This reaction mixture was stirred at 40 °C for 3 h, poured into ice water, and combined with dichloromethane. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving a crude oil. This crude product was purified by flushing a silica gel column with 3–5% ethyl acetate in benzene.

(3*E*)-4-(4-Phenoxyphenyl)but-3-en-2-one (55). NaOH (3 N; 2 mL) was added at the ice bath temperature to a solution of 4-phenoxybenzaldehyde (5.21 g, 26 mmol) in acetone (50 mL) and water (20 mL). This mixture was stirred for 6 h at room temperature, poured into ice water, and acidified with 1 N HCl. The pale yellow precipitate was collected by filtration and then recrystallized from aqueous ethanol, giving 5.37 g (87%) of **53**: ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3, $COCH_3$), 6.58 (d, 1, J = 17 Hz, =$CHCOCH_3$), 6.8–7.6 (m, 10).

(*E*)-*p*-Phenoxycinnamaldehyde (56). A mixture of 4-phenoxybenzaldehyde (1.33 g, 6.7 mmol) and (formylmethylene)triphenylphosphorane (Trippett and Walker, 1961) (2.16 g, 7.1 mmol) in benzene (50 mL) was stirred for 5 days at the refluxing temperature. After the removal of benzene in vacuo, *n*-hexane was added. The precipitate was separated by filtration. The filtrate was concentrated in vacuo and the residue applied to a silica gel column that then was flushed with benzene–ethyl acetate, giving 0.78 g (52%) of **56**: ^{1}H NMR ($CDCl_3$) δ 6.55 (dd, 1, J = 8 and 17 Hz, =CHCHO).

(3*E*)-4-(4-Phenoxyphenyl)but-3-en-2-one (*E*)-Oxime *O*-Propyl Ether (60). *O*-Propyl hydroxylammonium chloride (0.77 g, 6.9 mmol) was added to a solution of 55 (1.10 g, 4.6 mmol) in tetrahydrofuran (12 mL) at the ice bath temperature. After stirring it for 6 h, the reaction mixture was poured into ice water and combined with benzene. The extract obtained was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving an oily residue. This oil was applied to a silica gel column that then was eluted with benzene–hexane to obtain 0.78 g (57%) of *E*-**60**.

(*E*)-*p*-Phenoxycinnamaldehyde (*E*)-Oxime *O*-Propyl Ether (61). *O*-Propyl hydroxylammonium chloride (0.68 g, 6.1 mmol) was added to a solution of **56** (0.80 g, 3.6 mmol) in ethanol (10 mL) at the ice bath temperature. After stirring it for 12 h at room temperature, the reaction mixture was poured into ice water and treated with benzene. The extract formed was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving an oily risidue. This oil was applied to a silica gel column that then was treated with benzene–hexane giving 0.58 g (58%) of *E*-**61**.

(4-Benzylphenoxy)acetone (57). Bromoacetone (3.27 g, 24 mmol) was added slowly to a mixture of 4-benzylphenol (3.68 g, 20 mmol) and K_2CO_3 (2.8 g, 20 mmol) in acetone (20 mL) at room temperature. This reaction mixture was stirred for 12 h at room temperature, poured into ice water, and treated with ether. The ether layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo giving 6.43 g (96%) of **57** as a pale yellow solid.

(4-Benzylphenoxy)acetaldehyde Diethyl Acetal (58). 4-Benzylphenol (3.68 g, 20 mmol) and bromoacetaldehyde diethyl acetal (5.0 g, 25 mmol) were added to an ethanol solution (20 mL) in which sodium metal (0.50 g, 22 mmol) had been dissolved. This reaction mixture was refluxed for 30 h, poured into ice water, and treated with benzene. The extract obtained was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated in vacuo, giving 4.03 g (67%) of **58** as an oil.

(4-Benzylphenoxy)acetone (*E*)-Oxime *O*-Propyl Ether (62). *O*-Propyl hydroxylammonium chloride (0.80 g, 7.2 mmol) was added to a solution of **57** (1.0 g, 4.2 mmol) in ethanol (15 mL) at the ice bath temperature. This reaction mixture was stirred for 10 h at room temperature, poured into ice water, and treated with benzene. The extract obtained was washed with water, dried over $MgSO_4$, and concentrated in vacuo to an oily residue. This

residue was applied to a silica gel column that was treated with benzene–hexane and produced 0.88 g (71%) of *E*-**62**.

(4-Benzylphenoxy)acetaldehyde Oxime *O*-Propyl Ether (63). A water solution (5 mL) of *O*-propyl hydroxylammonium chloride (0.56 g, 5 mmol) and 1 N HCl (0.5 mL) was added to a solution of **58** (0.90 g, 3 mmol) in ethanol (20 mL). This mixture was stirred for 2 h at 70 °C, poured into ice water, and treated with benzene. The extract obtained was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving an oily residue that was applied to a silica gel column and eluted with benzene to obtain 0.73 g (86%) of **63**.

(4-Phenoxyphenoxy)acetaldehyde Diethyl Acetal (59). 4-Phenoxyphenol (3.72 g, 20 mmol) and bromoacetaldehyde diethyl acetal (4.33 g, 22 mmol) were added at room temperature to an ethanol solution (20 mL) in which sodium metal (0.50 g, 22 mmol) had been dissolved. This reaction mixture was refluxed for 30 h, poured into ice water, and treated with benzene. The extract obtained was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving 4.15 g (69%) of **59** as oil.

(4-Phenoxyphenoxy)acetaldehyde Oxime *O*-Propyl Ether (64). A water solution (5 mL) of *O*-propyl hydroxylammonium chloride (0.56 g, 5 mmol) and 1 N HCl (0.5 mL) was added to a solution of **59** (0.91 g, 3 mmol) in ethanol (20 mL) at the ice bath temperature. This reaction mixture was stirred for 3 h at 70 °C, poured into ice water, and treated with benzene. The extract obtained was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving an oily residue that was applied to a silica gel column and flushed with benzene to produce 0.83 g (97%) of **64**.

(4-Phenoxyphenoxy)acetaldehyde Oxime *O*-Allyl Ether (65). A mixture of *O*-allyl hydroxylamine (0.37 g, 5 mmol) and 2 N HCl (1.5 mL) was added to a solution of **59** (0.91 g, 3 mmol) in ethanol (20 mL) at the ice bath temperature. This reaction mixture was stirred for 10 h at 70 °C, poured into ice water, and treated with benzene. The extract obtained was washed with water, dried over $MgSO_4$, and concentrated in vacuo, giving an oily residue that was applied to a silica gel column and flushed with benzene to produce 0.79 g (93%) of **65**.

The analytical results for C, H, and N of these new compounds were within ±0.3% of the theoretical values.

Hydrophobicity Parameter log *P*. The hydrophobicity of the molecule is expressed by the logarithm of the partition coefficient between 1-octanol/water, log *P*. The method of estimation is essentially that used for the 2,4-dodecadienoate derivatives in our previous study (Nakayama et al., 1984): log *P*(9,10-unsubstituted *O*-ethyl oxime, **12**) = log $P(CH_3CH{=}NOH)$ + [log $P(C_6H_5CH{=}NOCH_3)$ − log $P(C_6H_5CH{=}NOH)$] + $12\pi(CH_3)$ + $F_{=}$ + $3F_{cBr}$ and log *P*(9-ene *O*-methyl oxime, **5**) = log *P*(**12**) − $\pi(CH_3)$ + $F_{=}$, for which $\pi(CH_3)$ (0.54) is the hydrophobicity parameter for the CH_3 substituent, $F_{=}$ (−0.55) is the fragmental factor for a double bond, and F_{cBr} (−0.13) the factor for a chain branch (Hansch and Leo, 1979). For the 9,10-unsubstituted and 9-ene *N*-methyl carbamates **33** and **27**, log *P*(**33**) = log $P(CH_3OC(O)NHCH_3)$ + $12\pi(CH_3)$ + $F_{=}$ + $3F_{cBr}$ and log *P*(**27**) = log *P*(**33**) + $F_{=}$. The log *P* values for the oxime *O*-ethers and carbamates with higher alkyls than those of the O- and N-substituents were calculated by adding the $\pi(CH_3)$ values consecutively.

For the 9,10-epoxy derivatives, log *P*(ethylene oxide) − log *P*(ethylene) was added to the value of the corresponding 9-ene compound. The log *P* for a 10-methoxy derivative was calculated by log *P*(corresponding 9,10-unsubstituted compound) + $\pi(OCH_3)$ + F_{gBr}, for which F_{gBr} (−0.22) is the group branch factor. The experimental data used for these calculations were taken from the literature (Hansch and Leo, 1979), except that for $\pi(OCH_3)$ the value of −0.98 reported by Iwasa et al. (1965) was used.

Bioassay Procedures. *Mosquito* (*Culex pipiens pallens Coquillett*). Fourth larval instars were selected from colonies maintained at 28 °C in water containing a diet mixture of mouse food and dry yeast. The eggs were a gift of Sumitomo Chemical Co., Ltd. Three replicates of 20 larvae each were transferred to disposable plastic tumblers containing 100 mL of water. Ethanol solutions of the test compounds then were added to the tumblers (10 μL/100 mL of water), after which the diet powder was added as food. The tumblers were covered with nylon net to prevent 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 the pupal cuticles. The nonemergence percentage of the control (no chemicals added except 10 μL/100 mL of ethanol) was less than 10%.

Rice Stem Borer (*Chilo suppressalis Walker*). Eggs of the rice stem borer, supplied by Takeda Chemical Co., Ltd., were hatched and reared on young rice plants grown in glass tumblers (7 cm × 13 cm) at 28 °C under long-day photoperiods (16L–8D). The last larval instars in the wandering stage, about 20 days after hatching, were collected and placed in petri dishes. A 1.0-μL portion of an ethanol solution of the compound to be tested was applied topically to the dorsal part of each of 20 larvae. A sheet of folded tissue paper, pleated for the insertion of the larvae pupate, was placed in a dish that then was covered with a glass cap. After 3–6 days at 28 °C, the paper and larvae that had not molted to pupae were removed. Results were scored as the percentage of unemerged adults, including those that could escape only partially from the pupal cuticles. The value for the control experiment was 0%.

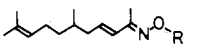
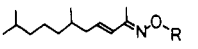
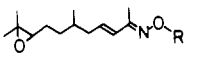
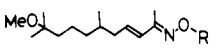
Housefly (*Musca domestica*). Ten last larval instars just before pupation ("prepupae") were placed in separate petri dishes. A 1.0-μL portion of an acetone solution of the compound to be tested was applied topically to the dorsal part of each prepupa. After 14 days at 25 °C, results were scoured as the percentage of unemerged adults, adults that could escape only partially from the pupal cuticules being included. The value for the control was 0%.

The experimental results in the bioassays were confirmed mostly by replication at concentrations at which high ratings (usually more than 50% inhibition of metamorphosis) were recorded, but experiments usually were not repeated at concentrations recorded for lower activity. When an abnormal rating was found, repetitions were made at that concentration and those near by. 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.

RESULTS AND DISCUSSION

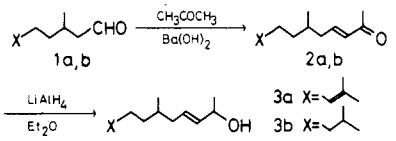
Synthesis of Compounds. *Undecen-2-one Oxime O-Ethers and Undecen-2-yl Carbamates.* The compounds prepared are listed in Tables I and II. Each class is divided into four subseries; 9-ene, 9,10-epoxy, 10-methoxy, 9,10-unsubstituted derivatives. The common starting compound for the first three, 6,10-dimethyl-3(*E*),9(*E*)-undecadien-2-one (**2a**), was prepared from (±)-citronellal (**1a**) and the source of the 9,10-unsubstituted derivatives, 6,10-dimethyl-3(*E*)-undecen-2-one (**2b**), from 3,7-dimethyloctanal (**1b**) by aldol condensation with acetone in an aqueous medium in the presence of barium hydroxide (Scheme I) (Streinz and Romanuk, 1981). This method

Table I. JH Activity of Undecen-2-one Oxime *O*-Ethers

		Culex pipiens, ppm			*Chilo suppressalis*, μg/larva			*Musca domestica*, μg/prepupa					
no.	R (compd)	10	1	0.1	100	10	1	200	50	13	3	0.8	log *P*
													
5	CH_3	29	9		13								5.10
6	CH_2CH_3	21	14		71	8	0	100	20				5.64
7	$CH_2CH_2CH_3$	44	14	10	94	21		50	30				6.18
8	$CH(CH_3)_2$	60	32	31	84	8	0	90	20				6.05
9	$CH_2CH(CH_3)_2$	75	24	17	70	29		20	0				6.59
10	$CH_2CH{=}CH_2$	67	31	20	100	57	17	50	20				5.63
11	$CH_2C{\equiv}CH$	97	39	19	100	47		80	60				4.76
													
12	CH_2CH_3	55	14	5	95	18		80	16				6.19
13a	$CH_2CH_2CH_3$	78	47	28	100	87	47	100	90	10			6.73
13b	$CH_2CH_2CH_3$ (*E*)[a]	29	0		50			20	0				6.73
14	$CH_2CH{=}CH_2$	67	26	21	100	51		80	85	<20			6.18
													
15	CH_3	89	3		64	39		10					3.67
16	CH_2CH_3	100	86	22	100	39		100	95	70	20		4.21
17	$CH_2CH_2CH_3$	100	100	10	100	91	21	100	100	65	70	30	4.75
18	$CH(CH_3)_2$	100	49	11	100	53	0	100	100	100	30		4.62
19	$CH_2CH_2CH_2CH_3$	100	79	18	100	29		100	60				5.29
20	$CH_2CH{=}CH_2$	100	98	3	100	56	8	100	100	90	30		4.20
21	$CH_2C{\equiv}CH$	100	83	6	100	26		100	95	90	30		3.33
													
22	CH_3	50	5										4.45
23a	CH_2CH_3	100	93	4	95	7		40	20				4.99
23b	CH_2CH_3 (*E*)[a]	29	0		36			20	20				4.99
24	$CH_2CH_2CH_3$	100	92	25	94	29		90	70	75	40	10	5.53
25	$CH_2CH{=}CH_2$	100	95	7	69	9		70	50				4.98
26	$CH_2C{\equiv}CH$	100	98	23	100	17		70	10				4.11
	(JH I)		100	70	100	86	67		20[b,c]				
	(Methoprene)			98	100[d]				100[d]				5.95

[a] *Z*-Oxime. [b] Did not reach 100% inhibition at 200 μg/prepupa. [c] At 25 μg. [d] At 0.1 μg.

Scheme I

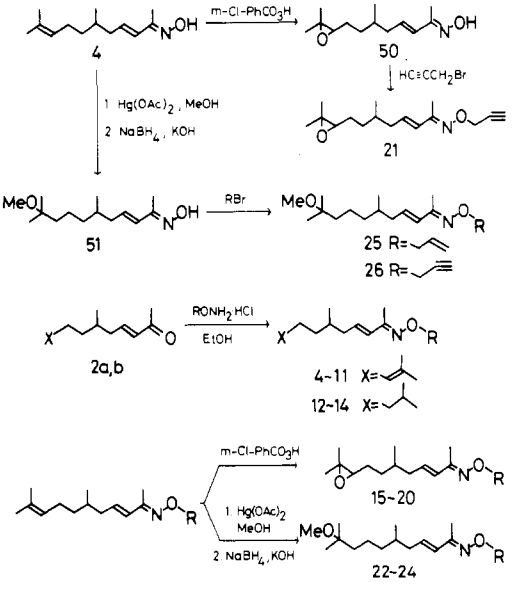


is much simpler than that reported previously, in which aldehydes and 2-oxopropyl phosphonate react (Henrick et al., 1975). These compounds and their derivatives are all racemic. The *E* configuration at the 3-double bond was identified by ^1H NMR.

Oxime **4** and oxime *O*-ethers **5**–**14** were obtained conventionally by condensation of ketones **2a** and **2b** with unsubstituted and appropriately O-substituted hydroxylamines (Scheme II). The geometric isomers of the ketoximes are indicated by the *E* and *Z* nomenclature used to designate the geometric relations of the groups around a double bond, taking the unshared pair of electrons at the nitrogen atom as the lowest priority group. Accordingly, the isomer with the methyl on the same side of double bond as the nitrogen substituent (OR) was designated an *E*-oxime and the one with the other geometry the *Z*-oxime.

The *E* and *Z* isomers of the oximes, i.e. *E*-oxime and *Z*-oxime, were separated by silica gel column chromatography. Their configurations were assigned by ^1H NMR spectroscopy, the signals of the C_3 hydrogen in the *E* isomer occurring at δ 5.9–6.0 and the signal of the C_3 hydrogen of the *Z* isomer shifting ca. 0.7 ppm to the lower field due to the anisotropic effect produced by the difference in oxime structure (Dvolaitzky and Dreiding, 1965; Slomp and Wechter, 1962; Benson and Pohland, 1965). Under

Scheme II

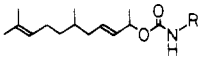
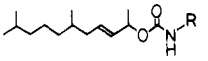
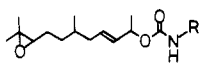
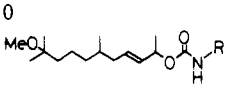


the reaction conditions shown in the Experimental Section, *E*-oximes were the predominant products, and the *E*/*Z* ratio was ca. 2/1.

Reduction of ketones **2a** and **2b** with $LiAlH_4$ gave α,β-unsaturated alcohols **3a** and **3b** (Scheme I), from which carbamates **27**–**32** were prepared by the reaction with appropriate isocyanates (Scheme III).

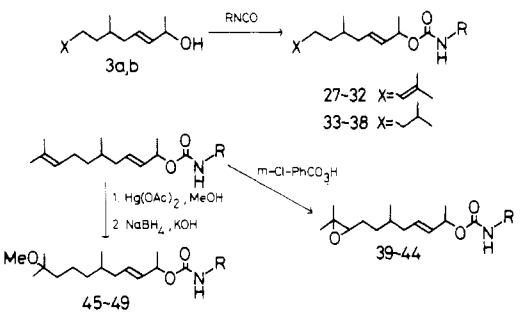
The epoxides **15**–**21**, **39**–**44**, and **50** were prepared by *m*-chloroperbenzoic acid oxidation of the corresponding

Table II. JH Activity of Undecen-2-yl Carbamates

no.	R (compd)	*Culex pipiens*, ppm 10	1	0.1	*Chilo suppressalis*, μg/larva 100	10	1	0.5	0.1	*Musca domestica*, μg/prepupa 200	50	13	3	0.8	log *P*
															
27	CH_3	83	35	5	93	7				90	0				4.93
28	CH_2CH_3	92	43	8	100	25				80	30				5.47
29	$CH_2CH_2CH_3$	88	18	15	82	18				10	20				6.01
30	$CH(CH_3)_2$	98	55	18	47					50	30				5.88
31	$CH_2CH_2CH_2CH_3$	46	11	2	23					20	20				6.55
32	C_6H_5	31	15		14					10	10				6.83
															
33	CH_3	92	24	18	100	38				20	20				5.48
34	CH_2CH_3	100	35	9	100	100	98	93	20	90	95	70	60	20	6.02
35	$CH_2CH_2CH_3$	97	18		100	50					10				6.56
36	$CH(CH_3)_2$	100	31	2	100	38				90	60				6.43
37	$CH_2CH_2CH_2CH_3$	55	18		30	0				10	0				7.10
38	C_6H_5	58	14		0					10	10				7.38
															
39	CH_3	100	86	13	100	64	27			30	20				3.50
40	CH_2CH_3	100	100	34		100	14			30	20				4.04
41	$CH_2CH_2CH_3$	100	84	13		100	7			20	10				4.58
42	$CH(CH_3)_2$	100	98	19	70	38				20	40				4.45
43	$CH_2CH_2CH_2CH_3$	91	26	9	35					40	0				5.12
44	C_6H_5	58	14		0					10	10				5.40
															
45	CH_3	100	10	23	72	69				10	20				4.28
46	CH_2CH_3	100	95	15	100	81	58	19		80	75	75	60	40	4.82
47	$CH_2CH_2CH_3$	100	15	0	69	11				10	0				5.36
48	$CH(CH_3)_3$	100	98	3	61	50				100	85	65	70	10	5.23
49	$CH_2CH_2CH_2CH_3$	93	5	7	8					10	0				5.90
	(JH I)		100	70	100	86	87				20[a,b]				
	(Methoprene)			98		100[c]					100[c]				5.95

[a] Did not reach 100% inhibition at 200 μg/prepua. [b] At 25 μg. [c] At 0.1 μg.

Scheme III



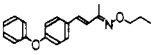
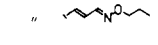
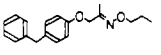
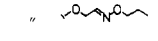
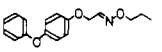
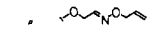
olefins and methoxy derivatives **22–24**, **45–49** and **51** by methoxy mercuration–demercuration according to Wakabayashi (1969) (Scheme II and III). The oxime *O*-allyl (**25**) and *O*-propargyl (**21** and **26**) ethers were prepared, respectively, by O-alkylation of the 9,10-epoxy (**50**) and 10-methoxy (**51**) oximes (Scheme II) that had been prepared from the O-unsubstituted precursor (**4**).

(Phenoxyphenoxy)acetaldehyde Oxime O-Ethers and Related Derivatives. The structures of the compounds prepared are shown in Table III.

Aldol condensation of 4-phenoxybenzaldehyde (**52**) with acetone gave 4-(4-phenoxyphenyl)but-3-en-2-one (**55**), the *E* configuration at the 3-double bond of which was identified by ^1H NMR. 4-Phenoxycinnamaldehyde (**56**) was obtained from **52** by the Wittig reaction with (formylmethylene)triphenylphosphorane that had been prepared by the method of Trippett and Walker (1961). The reaction of 4-benzylphenol (**53**) with bromoacetone in the presence of K_2CO_3 gave **57**. Ketones **55** and **57** and aldehyde **56** were converted conventionally to the corresponding *O*-propyl oximes **60–62** by their reactions with *O*-propyl hydroxylamine. The *E*-oximes that predominated in the reaction were separated by silica gel chromatography.

4-Benzyl- and (4-phenoxyphenoxy)acetaldehydes, **58** and **59**, were prepared by the reaction of bromoacetaldehyde diethyl acetal with 4-benzyl- and 4-phenoxyphenol, respectively, in the presence of NaOEt. The acetals then

Table III. JH Activity of 4-Phenoxy- and 4-Benzylphenyl Derivatives against *Culex pipiens*

no.	compd	% inhibn metamorphosis, ppm 1	0.1	0.01	0.001
60		100	26		
61		100	100	2	
62		100	94	26	
63[a]		100	100	80	37
64[a]		100	100	62	20
65[a]		100	86	79	
	JH I	100	70		
	Methoprene		98	94	81

[a] A mixture of *E*- and *Z*-oximes.

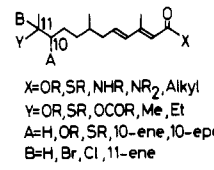
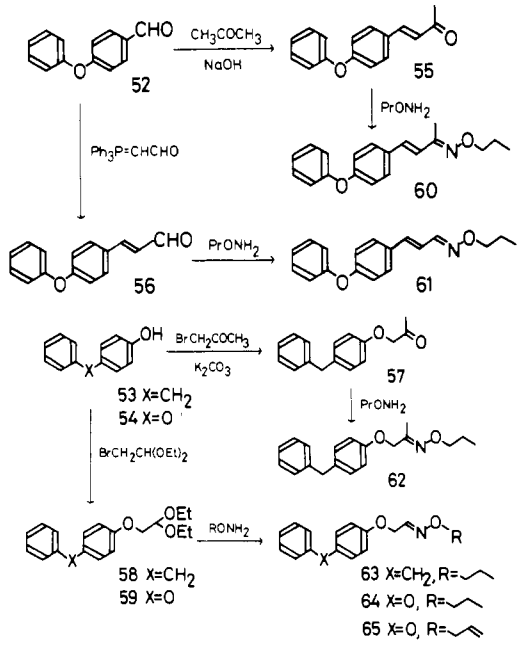


Figure 1. Structure of JH-active 2,4-dodecadienone derivatives.

Scheme IV



were allowed to react with appropriate alkoxyamines under acidic conditions to give the oxime *O*-ethers **63–65**. These compounds were bioassayed as mixtures of *E*- and *Z*-oximes because separation by conventional chromatographic techniques was difficult. The reactions are summarized in Scheme IV.

Biological Assay. Bioassays were made of affects of the oxime *O*-ethers **5–26** and carbamates **27–49** on synchronized sensitive stages of *C. pipiens*, *C. suppressalis*, and *M. domestica* and of the aromatic derivatives **60–65** on *C. pipiens*. Results are summarized in Tables I–III. Activities are expressed as the inhibition ratio (percent) of metamorphosis at each concentration (ppm, *C. pipiens*) or dose (μg/head, *C. suppressalis* and *M. domestica*). In each table, data for JH I and methoprene are included as references. Unless otherwise stated, the activity data for the oximes are for the 3(*E*)-undecen-2-one *E*-oximes. No 3(*Z*) isomers were included in the synthesis and thus in the bioassay of both the oximes and carbamates.

Structure–Activity Relationship. Our recent quantitative structure–activity analyses (Nakayama et al., 1984) of JH-active 2,4-dodecadienone types of compounds (Figure 1) showed that, in particular, the steric and hydrophobic properties of the molecule are highly related to activity against *A. aegypti* (yellow fever mosquito) and *T. molitor* (yellow mealworm). Structural features that are important for the expression of JH activity in both insect species are as follows: (1) the length of the whole molecule constructed by the CPK model and measured along the axis that passes through the C-1 and C-10 atoms in the extended conformation (Figure 1), the optimum for activity being estimated as ca. 21 Å; (2) the hydrophobicity of the entire molecule, the optimum value of which is 6–7 in terms of the logarithm of the partition coefficient between 1-octanol/water (log *P*), evidence that there is an optimal hydrophobic condition for activity; (3) the presence of an α-branch of the alcohol moiety of the ester derivatives (X = OR, SR in Figure 1), which supposedly prevents the hydrolytic attack of a metabolic enzyme on the ester carbonyl.

The total length and the steric dimensions at the oxime *O*-ether and carbamate ends of the undecene-2-one derivatives were designed so as to examine, or to study, the QSAR results. As the results, the activities of the oxime *O*-ethers that have *n*-propyl (**7, 13, 17, 24**), isobutyl (**9**), allyl (**10, 14, 20, 25**), or propargyl (**11, 21, 26**) at the ether moiety are generally higher than those having smaller or larger alkyls throughout the four subseries of compounds (9-ene, 9,10-unsubstituted, 9,10-epoxy, 10-methoxy derivatives) as well as throughut the three insect species *C. pipiens*, *C. suppressalis*, and *M. domestica* (Table I). A similar trend was observed for the carbamate series of compounds, *N*-ethyl (**28, 34, 40, 46**) and/or the *N*-isopropyl (**30, 36, 42, 48**) derivatives always being the most active compounds in each subclass (Table II). The total lengths of these active compounds correspond to the optimum value, ca. 21 Å, as described above, which suggests that the diameter of the JH receptor is common to all these insects. Compounds that have one carbon unit more, or less, are ca. 1.3 Å longer, or shorter, in total length, and their weaker activities appear to be attributable to this fact. The possibility of a common optimal length has been anticipated for a wide variety of active compounds as well as for a wide variety of insect species (Henrick et al., 1982).

E-Oximes, **13a** in the 9,10-unsubstituted and **23a** in the 10-methoxy series, were markedly more active than the corresponding *Z*-oximes, **13b** and **23b**, against three insect species. A similar trend was observed for the other series of compounds (data not shown). The lower activity of the *Z*-oximes is attributed to the bent *Z*-oxime structure which would not fit well into the receptor. The effect of the configuration at C-6 is obscure in the activity data because the compounds tested are racemic. The *S* isomer at the corresponding position (C-7 in Figure 1) of the 2,4-dodecadienone derivatives has been, however, reported to be more active than the *R* counterpart against some insects (Henrick et al., 1978). Also the effect has been suggested to be uniform for an insect species regardless of the structure of other parts of the molecule (Nakayama et al., 1984). The activity of the *S* isomers of the present compounds therefore may be higher than the values given in the tables.

In the oxime *O*-ethers, the activities of the 9,10-epoxy and 10-methoxy derivatives are considerably higher than the corresponding 9-ene and 9,10-unsubstituted derivatives (**17** vs. **7** and **24** vs. **13a**). A similar effect has been reported for the activity of the 2,4-dodecadienone series of compounds having the 11-alkoxy group against *A. aegypti* (Henrick et al., 1976), and the oxygen function is reported to enhance the binding of the compounds to the receptor via H bonding (Nakayama et al., 1984). In the carbamate series, the structural effect of the terpenoid end differed from the effects of the oxime *O*-ethers. For *C. pipiens*, the activities of the 9,10-epoxides and 10-methoxides tended to be only slightly higher than those of the 9-ene and 9,10-unsubstituted derivatives. For *C. suppressalis* and *M. domestica*, the activity of 9,10-unsubstituted and 10-methoxy compounds was higher than for the other two series of compounds. This apparent discrepancy is attributed to the difference in the hydrophobicity of the molecules.

The log *P* values of the oxime *O*-ethers and carbamates were estimated by the additive–constitutive rule (Hansch and Leo, 1979) and are listed in Tables I and II. The oxime

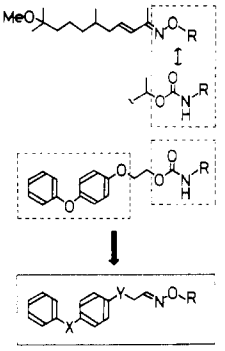


Figure 2. Schematic representation of the development of (4-phenoxyphenoxy)acetaldehyde oxime *O*-ethers and related compounds.

O-ethers are more hydrophobic than corresponding carbamates that have the same total lengths. The difference in the value is 0.71, exemplified by a comparison of epoxy *n*-propyl oxime **17** (4.75) and epoxy *N*-ethylcarbamate **40** (4.04). The log *P* value of the most active carbamate, 9,10-unsubstituted *N*-ethyl **34**, is 6.02, and the introduction of the oxygen function considerably lowers the value, for example to 4.04 for the less active **40**. The hydrophobicity of compound **40** appears to differ greatly from the optimum, whereas that of 9,10-unsubstituted **34** is much closer, making the latter compound relatively highly active. The most active oxime, **17**, has a considerably higher log *P* (a difference of 0.71) than **40** as well as the activity-enhancing epoxy substituent. The log *P* value of the corresponding 9,10-unsubstituted *n*-propyl oxime **13a** is 6.73, which is thought to be much above the optimum. This, together with the absence of the oxygen function, appears to lower its activity. Consideration of the hydrophobic condition together with the steric condition may provide a new insight into the structure–activity interpretations made previously that led to the development a new useful compound (Henrick et al., 1982).

The structure–activity profiles of oxime *O*-ethers and carbamates coincided well with the results of structure–activity analyses performed on the 2,4-dodecadienone series of compounds (Nakayama et al., 1984), evidence that the structure vs. activity relation of one class of compounds can be transposed to other types of compounds: Taken together, the results for the 2,4-dodecadienones and oxime and carbamate derivatives provide a guide with which to explore the structure vs. activity relations of diverse classes of JH-active compounds as well as with which to develop a new class of JH mimics. The activities of the most potent terpenoid oxime (**17**) and carbamate (**34**) are comparable to the activity of natural JH I against *C. pipiens* and *C. suppressalis* and much higher against *M. domestica* (Tables I and II). They are, however, much less potent than methoprene, the representative and most active member of the 2,4-dodecadienone family (Henrick et al., 1973). To obtain a compound having higher activity, we transposed the oxime structure to 2-(4-phenoxyphenoxy)ethyl carbamates that have been reported to show very high JH activity (Karrer and Farooq, 1981) and obtained (4-phenoxyphenoxy)acetaldehyde oxime types of compounds (**60–65**). The hybridization principle is shown schematically in Figure 2: The carbamate moiety of the (phenoxyphenoxy)ethyl carbamates overlaps that in our terpenoid carbamates, and the latter is convertible to terpenoid oximes. Therefore, the first and last sets of these compounds may be convertible.

Only effects on *C. pipiens* were investigated; results are summarized in Table III. Bioassays of effects on the other insect species will be made in the future. The activities of the 4-(benzylphenoxy)- and 4-(phenoxyphenoxy)acetaldehyde oxime *O*-ethers, **63–65**, were excellent, being more potent than JH I and as active as, or slightly less active than, methoprene in terms of 90–100% inhibition of metamorphosis. Compounds with a methyl at the α-position to the oxime nitrogen atom (**60** and **62**) were less active than their corresponding unsubstituted derivatives (**61** and **63**). This branch may prevent the proper steric fit to the receptor. The phenylpropenone derivatives, **60** and **61**, were about 10-fold less active than the corresponding phenoxyacetaldehyde oximes, whereas the exchange of the connecting link between the benzene rings from a methylene (**62, 63**) to an oxygen atom (**64, 65**) did not have a marked effect on activity. Investigation, using other compounds, of the detailed structural effects on variations in activity is a topic for future study.

ACKNOWLEDGMENT

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Registry No. (±)-**2a**, 99031-76-2; (±)-**2b**, 98901-22-5; **3a**, 98901-23-6; **3b**, 98901-24-7; (±)-**4** (isomer 1), 98901-25-8; (±)-**4** (isomer 2), 98901-87-2; (±)-**5** (isomer 1), 98901-26-9; (±)-**5** (isomer 2), 98901-88-3; (±)-**6** (isomer 1), 98901-27-0; (±)-**6** (isomer 2), 98901-89-4; (±)-**7** (isomer 1), 98901-28-1; (±)-**7** (isomer 2), 98901-90-7; (±)-**8** (isomer 1), 98901-29-2; (±)-**8** (isomer 2), 98901-91-8; (±)-**9** (isomer 1), 98901-30-5; (±)-**9** (isomer 2), 98901-92-9; (±)-**10** (isomer 1), 98901-31-6; (±)-**10** (isomer 2), 98901-93-0; (±)-**11** (isomer 1), 98901-32-7; (±)-**11** (isomer 2), 98901-94-1; (±)-**12** (isomer 1), 98901-33-8; (±)-**12** (isomer 2), 98901-95-2; (±)-**13a**, 98901-34-9; (±)-**13b**, 98901-35-0; (±)-**14** (isomer 1), 98901-36-1; (±)-**14** (isomer 2), 98901-96-3; **15**, 98901-37-2; **16**, 98901-38-3; **17**, 98901-39-4; **18**, 98901-40-7; **19**, 98901-41-8; **20**, 98901-42-9; **21**, 98921-34-7; (±)-**22** (isomer 1), 98901-43-0; (±)-**22** (isomer 2), 98901-80-5; (±)-**23a**, 98901-44-1; (±)-**23b**, 98901-45-2; (±)-**24** (isomer 1), 98901-46-3; (±)-**24** (isomer 2), 98901-81-6; (±)-**25** (isomer 1), 98901-47-4; (±)-**25** (isomer 2), 98901-82-7; (±)-**26** (isomer 1), 98921-35-8; (±)-**26** (isomer 2), 98921-38-1; **27**, 98901-48-5; **28**, 98901-49-6; **29**, 98901-50-9; **30**, 98901-51-0; **31**, 98901-52-1; **32**, 98901-53-2; **33**, 98901-54-3; **34**, 98901-55-4; **35**, 98901-56-5; **36**, 98901-57-6; **37**, 98901-58-7; **38**, 98901-59-8; **39**, 98901-60-1; **40**, 98901-61-2; **41**, 98901-62-3; **42**, 98901-63-4; **43**, 98901-64-5; **44**, 98901-65-6; **45**, 98901-66-7; **46**, 98901-67-8; **47**, 98921-36-9; **48**, 98901-68-9; **49**, 98901-69-0; **50**, 98921-37-0; (±)-**51** (isomer 1), 98901-70-3; (±)-**51** (isomer 2), 98901-83-8; **52**, 67-36-7; **53**, 101-53-1; **54**, 831-82-3; (*E*)-**55**, 98901-71-4; (*E*)-**56**, 98901-72-5; **57**, 51318-15-1; **58**, 98901-73-6; **59**, 53593-05-8; (*E,E*)-**60**, 98901-74-7; (*E,E*)-**61**, 98901-75-8; (*E*)-**62**, 98901-76-9; (*E*)-**63**, 98901-77-0; (*Z*)-**63**, 98901-84-9; (*E*)-**64**, 98901-78-1; (*Z*)-**64**, 98901-85-0; (*E*)-**65**, 98901-79-2; (*Z*)-**65**, 98901-86-1; $HONH_3^+Cl^-$, 5470-11-1; $MeONH_3^+Cl^-$, 593-56-6; $EtONH_3^+Cl^-$, 3332-29-4; $PrONH_3^+Cl^-$, 6084-54-4; *i*-$PrONH_3^+Cl^-$, 4490-81-7; *i*-$BuONH_3^+Cl^-$, 6084-58-8; $CH_2{=}CHCH_2ONH_3^+Cl^-$, 38945-21-0; $CH{\equiv}CCH_2ONH_3^+Cl$, 21663-79-6; MeNCO, 624-83-9; EtNCO, 109-90-0; PrNCO, 110-78-1; *i*-PrNCO, 1795-48-8; BuNCO, 111-36-4; PhNCO, 103-71-9; $BrCH_2Ac$, 598-31-2; $CH_2{=}CHCH_2ONH_2$, 6542-54-7; THF, 109-99-9; JHI, 13804-51-8; methoprene, 40596-69-8; bromoacetaldehyde diethyl acetal, 2032-35-1.

Supplementary Material Available: Tables of analytical data for undecen-2-one oxime *O*-ethers, undecen-2-yl carbamates, and 4-phenoxy- and 4-benzylphenyl derivatives (3 pages). Ordering information is given on any current masthead page.

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Methods for the Determination of Total Terbufos- [Phosphorodithioic Acid, *S*-(*tert*-Butylthio)methyl *O,O*-Diethyl Ester] Related Residues in Dermal Exposure Pads and Air-Collection Tubes and Related Alkyl Phosphate Metabolites in Urine

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Analytical methods are described that were used to estimate dermal and respiratory exposure of farmers to terbufos [phosphorodithioic acid, *S*-(*tert*-butylthio)methyl *O,O*-diethyl ester] while planting corn and applying COUNTER (American Cyanamid Co.) 15-G systemic insecticide–nematicide. Total terbufos-related compounds were extracted with acetone from both the gauze dermal patches and the XAD-2 resin used in air-collection tubes. These compounds were all oxidized with *m*-chloroperbenzoic acid to terbufos oxygen analogue sulfone, which was analyzed with a gas chromatograph equipped with a flame photometric detector. For the dermal pads, the validated limit of sensitivity was 0.2 μg/pad (5 ng/cm^2) and for the air samples it was 0.25 μg/tube. Recoveries from the dermal exposure pads ranged from 73 to 100% at fortification levels of 5–500 ng/cm^2, while recoveries from the air tubes ranged from 77 to 125% at levels of 0.4–500 ng/L. Terbufos-related alkyl phosphate esters in urine were determined by derivatization with pentafluorobenzyl bromide and gas chromatographic analysis using a flame photometric detector. Average recoveries of the three alkyl phosphates ranged from 85 to 113% at concentrations of 0.1–1.0 μg/ml.

COUNTER systemic insecticide–nematicide is an organophosphorus compound that has been commercially used on corn since 1975 to control a wide range of soil insects and nematodes. For corn use, it is formulated on montmorillonite clay and contains 15% active ingredient [terbufos: phosphorodithioic acid, *S*-(*tert*-butylthio)methyl *O,O*-diethyl ester]. To determine the level of exposure to farm workers loading and applying COUNTER 15-G at planting time, analytical methods were needed to estimate respiratory and dermal exposures and the degree of absorption by the farmer's body. Air-collection tubes filled with XAD-2 resin were used to estimate respiratory exposure while gauze pads were employed for dermal exposure. Urinary alkyl phosphate analysis was used to obtain an indication of absorption of the chemical.

Residue methods for the determination of total terbufos-related residues in various crops have previously been reported by Orloski (1980). These methods employed an oxidative step that would convert terbufos and its five potential, toxic metabolites (terbufos sulfoxide, terbufos sulfone, terbufoxon, terbufoxon sulfoxide, terbufoxon sulfone) to terbufoxon sulfone, which is determined gas chromatographically to give a total residue concentration. During loading and application of COUNTER 15-G, worker exposure would expect to be only to terbufos itself. However, to ensure a complete exposure appraisal, the dermal pads and air-collection tubes were analyzed for total terbufos-related compounds. Recoveries to validate the methods for pads and tubes were run with both terbufos and terbufos sulfoxide. Terbufos sulfoxide is the first oxidative soil metabolite and a representative of the other potential metabolites.

In addition to describing the methods used to estimate dermal and respiratory exposure, this paper also describes a method for analyzing urine for the presence of the diethyl phosphate hydrolytic metabolites. These analyses would give an indication of the absorption of terbufos due to the farm worker's total exposure.

EXPERIMENTAL PROCEDURES

Reagents. All solvents used were Burdick and Jacksons's distilled in glass brand. The oxidant, *m*-chloroperbenzoic acid, was purchased from Aldrich Chemical Co. A 10% solution of oxidant was prepared immediately before use by dissolving 1.0 g in 10 mL of methylene chloride. A 10% solution of polyethylene glycol 400 (PEG-400), USP, was prepared by diluting 1 mL of PEG-400 to 10 mL with acetone. Saturated solutions of sodium

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