Oxime Ethers: New Potent Insect Growth Regulators

Tadashi OHSUMI, Makoto HATAKOSHI, Hiroshi KISIDA,
Noritada MATSUO, Isamu NAKAYAMA
and Nobushige ITAYA

Pesticide Research Laboratory, Takarazuka Research Center,
Sumitomo Chemical Co., Ltd., Takarazuka 665, Japan

Received April 25, 1985

Oxime ethers containing a 4-phenoxyphenoxy group in the molecules were synthesized and their insect growth regulating (IGR) activities were studied. Of these new IGR's, propionaldehyde oxime *O*-2-(4-phenoxyphenoxy)ethyl ether and propionaldehyde oxime *O*-2-(4-phenoxyphenoxy)propyl ether were found to be most effective, having much higher activities than methoprene against larvae of *Culex pipiens pallens* and *Musca domestica* by the immersion method and medium method, respectively. In addition, the effects of steric isomerism of these compounds were examined; their IGR activities were found to have a close relationship to the juvenile hormone activity by the *Galleria* wax test.

Compounds with juvenile hormone (JH) activity can be expected to be potential insect growth regulators (IGR). A variety of terpenoid JH analogues such as methoprene¹⁾ have been introduced and some of them are now in practical use for the control of major insect pests.

In recent years, another class of JH analogues with a nonterpenoid structure have also been synthesized to show high IGR activities.^{2,3)}

Here, we report a new series of oxime ethers with outstanding IGR activities against larvae of *Culex pipiens pallens* (the common mosquito) and *Musca domestica* (housefly), and give some comments on their structure-activity relationship.

The synthesis of the oxime ethers (I~XV) is illustrated in Fig. 1. In procedure A, 4-substituted phenols (**1**) were etherified with α -halo esters to give phenoxy esters (**2**), which were then reduced with lithium aluminum hydride and followed by tosylation to give 4-substituted phenoxyalkyl tosylates (**4**). The tosylates **4** were then treated with oximes to give oxime ethers (**5**). In procedure B, oxime ethers (**7**) were synthesized by reacting oximes with 4-

substituted phenoxyalkyl bromides (**6**) prepared from **1** and alkylene dibromide. In procedure C, the bromide **6** was converted to 4-substituted phenoxyalkoxyamines (**9**) via *N*-(4-substituted phenoxyalkoxy)phthalimide (**8**), and then treated with carbonyl compounds to give **7**.

Compound III could be readily separated into the (*E*)- and (*Z*)-isomers (IIIa and IIIb) by column chromatography on silica gel using benzene as an eluent. An unequivocal assignment of their stereochemistry was accomplished with proton magnetic resonance (PMR) spectroscopy by correlating each vinyl proton signal with the corresponding vinyl proton signal for propionaldoxime.^{4,5)} Thus, the (*Z*) configuration was assigned to the isomer which exhibited its vinyl proton signal at δ 6.51 ppm, and the (*E*) configuration to the isomer whose vinyl proton signal was found downfield to the extent of 0.8 ppm in comparison with that for the (*Z*)-isomer.

The preparation of the optical isomers (IVa and IVb) is shown in Fig. 2. Ethyl L-lactate (**10**) was treated with *p*-toluenesulfonyl chloride to give (*S*)-ethyl 2-tosyloxypropionate (**11**), which was treated with 4-phenoxyphenol

Procedure A

Procedure B

Procedure C

FIG. 1. Syntheses of Oxime Ethers.

FIG. 2. Preparation of Optical Isomers of IV.

IVb was synthesized from ethyl D-lactate in a similar manner to that illustrated above.

to give (*R*)-ethyl 2-(4-phenoxyphenoxy)propionate (**12**). This ester (**12**) was reduced with lithium aluminum hydride and followed by tosylation to give (*R*)-2-(4-phenoxyphenoxy)propyl *p*-toluenesulfonate (**14**), which was then treated with propionaldehyde oxime to give (*R*)-propionaldehyde oxime O-2-(4-phenoxyphenoxy)propyl ether (IVa). The (*S*)-isomer (IVb) could be similarly prepared from ethyl D-lactate.

All the compounds synthesized were fully characterized by PMR spectrometry, elemental analysis for the C, H, and N atoms and/or

gas chromatographic analysis.

All the oxime ethers tested were isomeric mixtures unless otherwise specified.

Among the aldoxime ethers listed in Table I, the propionaldoxime ether (III) showed the highest activity against *C. pipiens*, and was also very active against *M. domestica*. The acetaldoxime ether (I) showed high activity against *M. domestica* (fifty times as active as methoprene), but its activity against *C. pipiens* was much less. On the other hand, the aldoxime ethers with longer alkyl groups (VI and VII) showed low activities against both of the insect

TABLE I. IC₅₀ VALUES OF OXIME ETHERS

Compound	R ₁	R ₂	R ₃	R ₄	<i>C. pipiens</i> IC ₅₀ (× 10 ⁻³ μmol/liter)	<i>M. domestica</i> IC ₅₀ (μmol/liter)
I	H	H	Me	H	0.37	0.044
II	Me	H	Me	H	4.5	0.074
III	H	H	Et	H	0.00013	0.28
IIIa		(E)-Isomer of III			0.00032	—
IIIb		(Z)-Isomer of III			0.00013	—
IV	Me	H	Et	H	0.0011	0.24
V	H	Me	Et	H	0.18	0.48
VI	H	H	<i>n</i> -Pr	H	0.17	0.73
VII	H	H	<i>n</i> -Bu	H	4.0	9.2
VIII	H	H	Me	Me	0.14	—
IX	H	H	Me	Et	0.84	—
X	H	H	Me	SMe	0.32	—
Methoprene					1.5	2.4

species. As already mentioned, the substituent R₃ must have a certain length for these oxime ethers to obtain high activities against each of the insect species. This may have some relation to the results^{6~8)} obtained for the farnesoate-type analogues, which indicated the variable effect of ester groups on the JH activity in different insect species.

It is interesting that the introduction of a methyl group into the ethylene group in III to give compound IV resulted in some decrease in activity against *C. pipiens* and a little increase in activity against *M. domestica*. In contrast, the introduction of a methyl group into the ethylene group in I to give compound II resulted in some decrease in the activities against both of the insect species. The placement of a methyl group at the carbon atom adjacent to the oxime ether group of III produced compound V with lower activities against both of the insect species in comparison with III. To our surprise, both of the geometrical isomers (IIIa and IIIb) were very active against *C. pipiens* and there was less difference in activity between the two isomers than we expected from the results⁹⁾ obtained for ethyl 3,7,11-trimethyl-2,4-dodecadienoate.

The activity of the ketoxime ethers (VIII, IX

and X) was much lower than that of III. For these oxime ethers, the bulkiness of the substituents R₃ and R₄ appeared to be very important, and highly active compounds were produced when one of them was a hydrogen atom.

The ethylene group of III was then successively replaced with longer alkylene chains as shown in Table II. The dependence of the activities of the aldoxime ethers on the alkylene chain length was apparent and their activities decreased rapidly as the number of carbon atoms constituting the alkylene chains was increased from 2 to 5. Concerning the influence of the linkage between two phenyl groups on the activity, highly active compounds were obtained when X was an oxygen atom or a methylene group, but not when X was a sulfur atom.

The optical isomers of IV were next examined. The activities of IVa and IVb were measured for *M. domestica* to show that the (*R*)-isomer (IVa, 89.7% enantiomeric excess) was more active than the (*S*)-isomer (IVb, 86.0% enantiomeric excess) (Table III).

Table IV lists the activity of III and IV by a *Galleria* wax test¹⁰⁾ in comparison with that of methoprene, showing the extremely high activity of these compounds. These results suggest that the high IGR activity of these oxime

TABLE II. ACTIVITIES OF PROPIONALDOXIME ETHERS WITH VARIOUS LINKAGES

Compound	<i>n</i>	X	<i>C. pipiens</i> IC ₅₀ (× 10 ⁻³ μmol/liter)	<i>M. domestica</i> IC ₅₀ (μmol/liter)
III	2	O	0.00013	0.28
XI	3	O	0.17	> 10
XII	4	O	5.1	> 10
XIII	5	O	31	> 10
XIV	2	CH ₂	0.000088	0.28
XV	2	S	0.33	> 10

TABLE III. IC₅₀ VALUES OF OPTICAL ISOMERS OF IV

Compound	Optical isomer (enantiomeric excess)	<i>M. domestica</i> IC ₅₀ (μmol/liter)
IV	(<i>RS</i>)	0.24
IVa	(<i>R</i>) (89.7%)	0.20
IVb	(<i>S</i>) (86.0%)	1.1

TABLE IV. ACTIVITY OF COMPOUNDS III AND IV IN THE *Galleria* WAX TEST

Compound	R	ID ₅₀ (× 10 ⁻³ μmol/pupa)	Relative activity
III	H	0.000084	83000
IV	Me	0.0012	5900
Methoprene		7.1	1

ethers is closely related to their JH activity.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus. PMR spectra were recorded at 60 MHz with a Hitachi R-24B high resolution spectrometer. Refractive indexes were determined with a Atago Abbe refractometer. Gas chromatographic analysis was carried out with a Shimadzu GC-7A gas chromatograph. Experiments are given by general procedures except for the syntheses of IVa and IVb.

4-Substituted phenoxy esters (2)—Procedure A. To a solution of 4-substituted phenol (50 mmol) and an α -halo

ester (60 mmol) in *N,N*-dimethylformamide (DMF) was added anhydrous potassium carbonate (8.28 g), the mixture being stirred at 100°C for 8 hr. The reaction mixture was diluted with ethyl acetate, and washed with water, dilute hydrochloric acid and water. The solvent was evaporated to give **2**.

4-Substituted phenoxyalkanols (3)—Procedure A. To a suspension of lithium aluminum hydride (1.5 g) in ether was added **2** (50 mmol) in ether with stirring at 0°C, the mixture being left overnight at room temperature. The reaction mixture was slowly added to cold dilute hydrochloric acid, washed with water and concentrated to give **3**.

4-Substituted phenoxyalkyl tosylates (4)—Procedure A. To a solution of **3** (24.4 mmol) in pyridine (30 ml) was added *p*-toluenesulfonyl chloride (5.61 g) with stirring at -5°C~0°C, the mixture being left overnight at room temperature. The resulting solution was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and concentrated to give **4**.

Oxime O-(4-substituted phenoxy)alkyl ethers (5)—Procedure A. Sodium hydride (30 mmol) was added to a solution of oxime (30 mmol) in DMF, and the mixture was stirred at 0°C for 1 hr. To the resulting solution was added a solution of **4** (25 mmol) in DMF at 0°C, the mixture being stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and washed with water, dilute hydrochloric acid and water. After evaporating the solvent, the residue was chromatographed on silica gel to give **5**.

4-Substituted phenoxyalkyl bromides (6)—Procedure B. To a mixture of **1** (26.9 mmol), alkylene dibromide (32.3 mmol) and water (36 ml) was added a solution of sodium hydroxide (1.02 g) in water (7 ml) with stirring at 100°C, the mixture being stirred under reflux until acidic. The resulting solution was extracted with ether, and the extracts were washed with water and concentrated to give **6**.

N-(4-Substituted phenoxyalkoxy)phthalimide (8)—Procedure C. A solution of *N*-hydroxyphthalimide (1.46 g), triethylamine (0.91 g) and **6** (8.14 mmol) in DMF was stirred at 100°C for 8 hr. The reaction mixture was poured into cold water and extracted with ethyl acetate. The extracts were washed with water and concentrated to give **8**.

4-Substituted phenoxyalkoxyamines (9)—Procedure C. To a mixture of hydroxylamine sulfate (0.27 g), **8** (3.16 mmol), tetra-*n*-butyl ammonium bromide (TBAB, 0.10 g), toluene (1.7 ml) and water (0.5 ml) was added a solution of sodium hydroxide (0.26 g) in water (0.5 ml)

with stirring at room temperature. The reaction mixture was stirred for 3 hr at the same temperature and extracted with ether. The extracts were washed with water and concentrated to give **9**.

Oxime O-(4-substituted phenoxy)alkyl ethers (7)—Procedure C. The compounds **7** were synthesized from **6** by the same procedure as that described for the preparation of **5**. Another synthesis of **7** from **9** was as follows.

To a mixture of **9** (10 mmol), TBAB (0.2 g), toluene (15 ml) and water (5 ml) was added a solution of a carbonyl compound (11 mmol) in toluene (5 ml) with stirring at room temperature. The reaction mixture was stirred for 3 hr at the same temperature and extracted with toluene. The extracts were washed with water, cold dilute hydrochloric acid and water. After evaporating the solvent, the residue was chromatographed on silica gel to give **7**.

(E)- and (Z)-Propionaldoxime O-2-(4-phenoxyphenoxy)ethyl ether (IIIa and IIIb). The separation of III into its geometrical isomers was readily accomplished by column chromatography on silica gel using benzene as an eluent. The (*E*) configuration was assigned to the isomer with the higher *R_f* value and the (*Z*) configuration to the other with the lower *R_f* value. Each isomer was over 99 percent pure by high-performance liquid chromatographic analysis [column, Lichrosorb SI-60 (E. Merck); mobile phase, *n*-hexane-chloroform-ethanol (500:25:2)].

(S)-Ethyl 2-tosyloxypropionate (11). To a solution of ethyl L-lactate (5.0 g) in pyridine (12 ml) was added *p*-toluenesulfonyl chloride (9.3 g) with stirring at -20°C , the mixture being left at 0°C for 2 days. The resulting solution was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and concentrated to give **11**. Yield 80%. PMR (CDCl_3) δ : 1.18 (3H, t, $J=7.0$ Hz), 1.49 (3H, d, $J=7.0$ Hz), 2.40 (3H, s), 4.04 (2H, q, $J=7.0$ Hz), 4.46 (1H, q, $J=7.0$ Hz), 7.0~7.7 (4H, m). $n_D^{25.5}$ 1.4983. $[\alpha]_D^{23.0} = -26.7^{\circ}$ (CHCl_3 , $c=1.10$).

(R)-Ethyl 2-(4-phenoxyphenoxy)propionate (12). To a solution of **11** (3.0 g) and 4-phenoxyphenol (2.5 g) in acetonitrile (30 ml) was added anhydrous potassium carbonate (1.5 g), the mixture being stirred at room temperature for 10 days. The reaction mixture was diluted with ethyl acetate, and washed with water, dilute hydrochloric acid and water. After evaporating the solvent, the residue was chromatographed on silica gel [eluent, *n*-hexane-ethyl acetate (20:1)] to give **12**. Yield 95%. PMR (CDCl_3) δ : 1.20 (3H, t, $J=7.0$ Hz), 1.55 (3H, d, $J=7.0$ Hz), 4.15 (2H, q, $J=7.0$ Hz), 4.61 (1H, q, $J=7.0$ Hz), 6.8~7.4 (9H, m). $n_D^{24.0}$ 1.5345. $[\alpha]_D^{24.0} = +31.8^{\circ}$ (CHCl_3 , $c=0.51$).

(R)-2-(4-Phenoxyphenoxy)propanol (13). To a suspen-

sion of lithium aluminum hydride (0.18 g) in ether was added **12** in ether with stirring at 0°C , the mixture being stirred for 1 hr at the same temperature. The reaction mixture was slowly added to cold ammonium chloride solution and extracted with ether. The extracts were washed with water and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated to give **13**. Yield 98%. PMR (CDCl_3) δ : 1.32 (3H, d, $J=6.0$ Hz), 3.75 (2H, d, $J=5.0$ Hz), 4.47 (1H, m), 6.7~7.5 (9H, m). $n_D^{24.5}$ 1.5678. $[\alpha]_D^{24.0} = -32.6^{\circ}$ (CHCl_3 , $c=0.56$). 89.7% enantiomeric excess.

The optical purity of **13** was determined by high-performance liquid chromatographic analysis [column, Sumipax OA-2300 (Sumika Chemical Analysis Service Ltd., Japan; mobile phase, isopropanol-*n*-hexane (1:99)].

(R)-2-(4-Phenoxyphenoxy)propyl tosylate (14). This compound was prepared by the same procedure as that described for the preparation of **11**. Yield 83%. PMR (CDCl_3) δ : 1.28 (3H, d, $J=6.0$ Hz), 2.38 (3H, s), 4.05 (2H, d, $J=5.0$ Hz), 4.40 (1H, m), 6.6~7.7 (13H, m).

(R)-Propionaldehyde oxime O-2-(4-phenoxyphenoxy)propyl ether (IVa). This compound was prepared by the same procedure as that described for the preparation of **5**. Yield 53%. $[\alpha]_D^{24.0} = -24.0^{\circ}$ (CHCl_3 , $c=0.45$).

(S)-Propionaldehyde oxime O-2-(4-phenoxyphenoxy)propyl ether (IVb). This compound was prepared from ethyl D-lactate by the same procedure as that already described. $[\alpha]_D^{24.0} = +28.0^{\circ}$ (CHCl_3 , $c=0.2$). 86.0% enantiomeric excess.

Bioassay procedures on *C. pipiens* and *M. domestica*

C. pipiens. An emulsifiable concentrate of each compound [xylene-Sorpol 3005X-active ingredient (5:2:1 by weight)] was diluted with water to obtain serial concentrations. The dilution (0.5 ml) was added to 100 ml of deionized water in a plastic cup. Twenty of the last instar larvae of *C. pipiens* were released into the cup and kept at 25°C with a diet until adult emergence. The rate of normal adult emergence was observed and corrected for that of the untreated one. IC_{50} (concentration required to produce 50% inhibition) was calculated by the probit method.

M. domestica. Powdered animal feed (2 g) was thoroughly mixed with bran (14 g). An emulsifiable concentrate obtained in the same way was diluted with water to obtain the desired concentrations and was added to the mixture. The resulting mixture was stirred well to make an artificial culture. Thirty of the 4-day-old larvae of *M. domestica* were reared until pupation. The pupae obtained were placed into a plastic cup and the rate of adult emergence was observed. IC_{50} was calculated as in the previous case.

Acknowledgments. We wish to express our special

thanks to Professor T. Fujita of Kyoto University for his invaluable suggestions. Thanks are also given to Mr. M. Nagase for high-performance liquid chromatographic analysis and Misses I. Fujimoto and H. Fukushima for their skillful work in bioassays.

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