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Synthesis and Structure–Activity Relationships of 6–Methyl–3–pyridyl Ethers as Anti–juvenile Hormone Agents

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A series of 6–methyl–3–pyridyl 2–(substituted phenoxy)ethyl ethers and related compounds were synthesized and evaluated against 72–hour old 3 rd–instar larvae of the silkworm, *Bombyx mori*, for their activity to induce precocious metamorphosis. A chloro substituent at the 3–position on the benzene ring and chain length of two carbon atoms between the two oxygen atoms were important for this activity. Replacement of 6–methyl–3–pyridyl portion with 3–pyridyl or various substituted pyridyl groups completely eliminated the activity, indicating that the 6–methyl–3–pyridyl ether moiety was indispensable for the activity. Of the compounds tested, 2–(3–chlorophenoxy)ethyl 6–methyl–3–pyridyl ether (**1**) was the most effective. Precocious metamorphosis induced by compound **1** was accompanied by the prolongation of the larval period and could be fully counteracted by methoprene, a juvenile hormone agonist.

INTRODUCTION

Since insect juvenile hormones (JHs) are very important in regulating metamorphosis, reproduction, diapause and behavior, compounds with anti–JH activity would be a prospective method for selective insect control as well as an effective tool in studies of insect physiology (Staal, 1986).

Ethyl 4–[2–(*t*–butylcarbonyloxy)butoxy]benzoate (ETB) is known to show anti–JH activity for the tobacco hornworm, *Manduca sexta* (Staal, 1982), and the silkworm, *Bombyx mori* (Kiguchi *et al.*, 1984). By modifying the structure of ETB, we have recently found out that 2–(3–chlorophenoxy)ethyl 6–methyl–3–pyridyl ether (**1**) induces precocious metamorphosis in the larvae of the silkworm, which is clearly recognized as a JH–deficiency symptom (Kim *et al.*, 2001). However, there was a quite difference in critical times between ETB and compound **1** treatment for induction of precocious metamorphosis; ETB was active only when applied to newly molted 3 rd–instar larvae, while compound **1** induced precocious metamorphosis when applied to larvae from 24 hr–old 3 rd–instar to 24 hr–old 4 th–instar. This result strongly indicates that the mode of action of compound **1** is different from that of ETB.

On the other hand, we have previously reported that 5–(4–propylphenoxy)pentyl 3–pyridyl ether (**2**) induces precocious metamorphosis in the silkworm (Kuwano *et al.*,

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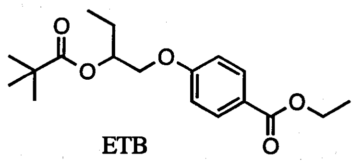
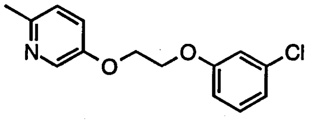
1998). The structure–activity relationship studies indicated that the presence of a 3–pyridine ring was essential for the activity, however, the introduction of a methyl group at the 6–position of the pyridine ring (compound **3**) completely eliminated the activity.

On the basis of these results, compound **1** appears to be a novel class of anti–JH agent. In this paper we describe details of the preparation and structure–activity relationships of a number of 6–methyl–3–pyridyl ethers and related compounds.



ETB



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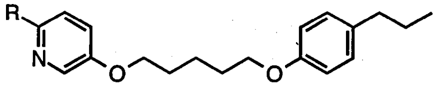


2 : R = H
3 : R = CH_3

MATERIALS AND METHODS

Chemicals

All melting points (mp) are uncorrected. ^{1}H NMR spectra were recorded on JEOL EX–400 spectrometer, using tetramethylsilane as an internal standard, and all samples were prepared in deuterochloroform. Pyriproxyfen was kindly supplied by Sumitomo Chemical Co. Compound **1** was synthesized according to the procedure reported previously (Kim *et al.*, 2001); Reaction of 2–(3–chlorophenoxy)ethyl bromide with 2–methyl–5–hydroxypyridine. Compound **4** was prepared according to reported methods (Kim and Kuwano, 2001).

Compounds **5–8**, **10–20** and **23–30** were prepared in the same manner as that used for compound **1** from the corresponding 2–(substituted phenoxy)alkyl bromides and hydroxypyridines instead of 2–(3–chlorophenoxy)ethyl bromide and 2–methyl–5–hydroxypyridine, respectively.

*6–Methyl–3–pyridyl 2–phenoxyethyl ether (**5**)*

mp 70–71 °C. ^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 4.32–4.36 (4H, m, $-(CH_2)_2-$), 6.94–7.00 (3H, m, phenyl), 7.07 (1H, d, J=8.8 Hz, pyridyl), 7.17 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 7.28–7.30 (2H, m, phenyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2–(2–Chlorophenoxy)ethyl 6–methyl–3–pyridyl ether (**6**)*

mp 68 °C. ^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 4.38–4.41 (4H, m, $-(CH_2)_2-$), 6.93 (1H, t, J=7.3 Hz, phenyl), 6.97 (1H, d, J=7.3 Hz, phenyl), 7.07 (1H, d, J=8.8 Hz, pyridyl), 7.20–7.25 (2H, m, phenyl and pyridyl), 7.37 (1H, dd, J=7.3, 2.0 Hz, phenyl), 8.25 (1H, d, J=2.9Hz, pyridyl).

*2-(4-Chlorophenoxy)ethyl 6-methyl-3-pyridyl ether (**7**)*
mp 130°C. ^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 4.26–4.35 (4H, m, $-(CH_2)_2-$), 6.87 (2H, d, J=7.8 Hz, phenyl), 7.08 (1H, d, J=8.8 Hz, pyridyl), 7.17 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 7.24 (2H, d, J=7.8 Hz, phenyl), 8.24 (1H, d, J=2.9 Hz, pyridyl).

*3-(3-Chlorophenoxy)propyl 6-methyl-3-pyridyl ether (**8**)*
^{1}H NMR δ : 2.27 (2H, quint, J=7.3 Hz, $-CH_2-$), 2.49 (3H, s, $-CH_3$), 4.11–4.20 (4H, m, $-(CH_2)_2-$), 6.79 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.92–6.95 (2H, m, phenyl), 7.05 (1H, d, J=8.8 Hz, pyridyl), 7.11 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 7.19 (1H, t, J=7.3 Hz, phenyl), 8.20 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Fluorophenoxy)ethyl 6-methyl-3-pyridyl ether (**10**)*
mp 48–49°C. ^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 4.30–4.34 (4H, m, $-(CH_2)_2-$), 6.66–6.74 (2H, m, phenyl), 7.08 (1H, d, J=8.8 Hz, pyridyl), 7.17–7.26 (3H, m, 2 phenyl and pyridyl), 8.25 (1H, d, J=2.9 Hz, pyridyl),

*2-(3-Bromophenoxy)ethyl 6-methyl-3-pyridyl ether (**11**)*
mp 81–83°C. ^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 4.31–4.33 (4H, m, $-(CH_2)_2-$), 6.88 (1H, dd, J=7.8, 2.0 Hz, phenyl), 7.07–7.18 (5H, m, phenyl and pyridyl), 8.24 (1H, d, J=2.9 Hz, pyridyl).

*6-Methyl-3-pyridyl 2-(3-trifluoromethylphenoxy)ethyl ether (**12**)*
mp 57°C. ^{1}H NMR δ : 2.52 (3H, s, $-CH_3$), 4.37 (4H, m, $-(CH_2)_2-$), 7.09–7.29 (5H, m, phenyl and pyridyl), 7.41 (1H, t, J=7.8 Hz, phenyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Methylphenoxy)ethyl 6-methyl-3-pyridyl ether (**13**)*
mp 67–68°C. ^{1}H NMR δ : 2.33 (3H, s, $-CH_3$), 2.50 (3H, s, $-CH_3$), 4.29–4.35 (4H, m, $-(CH_2)_2-$), 6.74–6.81 (2H, m, phenyl), 7.07 (1H, d, J=8.8 Hz, pyridyl), 7.16–7.21 (3H, m, phenyl and pyridyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Ethylphenoxy)ethyl 6-methyl-3-pyridyl ether (**14**)*
mp 142°C. ^{1}H NMR δ : 1.23 (3H, t, J=7.3 Hz, $-CH_3$), 2.50 (3H, s, $-CH_3$), 2.63 (2H, q, J=7.3 Hz, $-CH_2-$), 4.31–4.36 (4H, m, $-(CH_2)_2-$), 6.75–6.84 (3H, m, phenyl), 7.07 (1H, d, J=8.8 Hz, pyridyl), 7.16–7.23 (2H, m, phenyl and pyridyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Methoxyphenoxy)ethyl 6-methyl-3-pyridyl ether (**15**)*
^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 3.79 (3H, s, $-CH_3$), 4.15–4.35 (4H, m, $-(CH_2)_2-$), 6.51–6.56 (3H, m, phenyl), 7.07 (1H, d, J=8.8 Hz, pyridyl), 7.16–7.21 (2H, m, phenyl and pyridyl), 8.24 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Isopropylphenoxy)ethyl 6-methyl-3-pyridyl ether (**16**)*
mp 40°C. ^{1}H NMR δ : 1.24 (6H, d, J=7.3 Hz, $-(CH_3)_2$), 2.50 (3H, s, $-CH_3$), 2.87 (1H, q, J=7.3 Hz, methine), 4.32–4.36 (4H, m, $-(CH_2)_2-$), 6.76 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.84–6.87 (2H, m, phenyl), 7.07 (1H, d, J=8.8 Hz, pyridyl), 7.17–7.24 (2H, m, phenyl and pyridyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2-(2,3-Dichlorophenoxy)ethyl 6-methyl-3-pyridyl ether (**17**)*
mp 108–111°C. ^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 4.38–4.42 (4H, m, $-(CH_2)_2-$), 6.90 (1H, d, J=7.8 Hz, phenyl), 7.06–7.25 (4H, m, phenyl and pyridyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2-(2,5-Dichlorophenoxy)ethyl 6-methyl-3-pyridyl ether (**18**)*
mp 94–99°C. ^{1}H NMR δ : 2.50 (3H, s, $-CH_3$), 4.37–4.41 (4H, m, $-(CH_2)_2-$), 6.92 (1H, dd, J=7.8, 2.03 Hz, phenyl), 7.00 (1H, d, J=2.0 Hz, phenyl), 7.08 (1H, d, J=8.8 Hz, pyridyl), 7.21 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 7.29 (1H, d, J=7.3 Hz, phenyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2-(3,5-Dichlorophenoxy)ethyl 6-methyl-3-pyridyl ether (**19**)*
mp 97–99 °C, ^{1}H NMR δ: 2.50 (3H, s, $-CH_3$), 4.29–4.35 (4H, m, $-(CH_2)_2-$), 6.85 (2H, d, J=2.0 Hz, phenyl), 6.99 (1H, d, J=2.0 Hz, phenyl), 7.08 (1H, d, J=8.8Hz, pyridyl), 7.16 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 8.24 (1H, J=2.9 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 3-pyridyl ether (**20**)*
mp 75 °C. ^{1}H NMR δ: 4.32–4.41 (4H, m, $-(CH_2)_2-$), 6.84 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.95–6.98 (2H, m, phenyl), 7.20–7.29 (3H, m, phenyl and pyridyl), 8.26 (1H, d, J=2.9 Hz, pyridyl), 8.37 (1H, d, J=8.8 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 2-methyl-3-pyridyl ether (**23**)*
mp 62 °C. ^{1}H NMR δ: 2.47 (3H, s, $-CH_3$), 4.31–4.37 (4H, m, $-(CH_2)_2-$), 6.85 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.97–6.98 (2H, m, phenyl), 7.11–7.13 (2H, m, pyridyl), 7.22 (1H, t, J=7.8 Hz, phenyl), 8.11 (1H, d, J=8.8 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 2-iodo-6-methyl-3-pyridyl ether (**24**)*
^{1}H NMR δ: 2.50 (3H, s, $-CH_3$), 4.33–4.39 (4H, m, $-(CH_2)_2-$), 6.86 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.96–7.05 (3H, m, phenyl and pyridyl), 7.22–7.24 (2H, m, phenyl and pyridyl).

*2-(3-Chlorophenoxy)ethyl 2-chloro-3-pyridyl ether (**25**)*
mp 86–88 °C. ^{1}H NMR δ: 4.40 (4H, m, $-(CH_2)_2-$), 6.85 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.97–6.99 (2H, m, phenyl), 7.22–7.31 (3H, m, phenyl and pyridyl), 8.04 (1H, d, J=8.8 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 5-chloro-3-pyridyl ether (**26**)*
mp 63–64 °C. ^{1}H NMR δ: 4.34–4.37 (4H, m, $-(CH_2)_2-$), 6.83 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.95–6.99 (2H, m, phenyl), 7.21–7.29 (2H, m, phenyl and pyridyl), 8.23–8.26 (2H, m, pyridyl).

*2-(3-Chlorophenoxy)ethyl 6-methyl-2-pyridyl ether (**27**)*
^{1}H NMR δ: 2.52 (3H, s, $-CH_3$), 4.31–4.42 (4H, m, $-(CH_2)_2-$), 6.05 (1H, d, J=8.8 Hz, pyridyl), 6.45 (1H, d, J=8.8 Hz, pyridyl), 6.74 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.86 (1H, d, J=2.0 Hz, phenyl), 6.92 (1H, d, J=7.8 Hz), 7.15 (1H, t, J=7.8 Hz, phenyl), 7.25 (1H, d, J=8.8 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 6-chloro-2-pyridyl ether (**28**)*
mp 57–61 °C. ^{1}H NMR δ: 4.30 (2H, t, J=7.3 Hz, $-CH_2-$), 4.67 (2H, t, J=7.3 Hz, $-CH_2-$), 6.71 (1H, d, J=8.8 Hz, pyridyl), 6.84 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.92–6.96 (3H, m, phenyl and pyridyl), 7.21 (1H, d, J=7.8 Hz, phenyl), 7.54 (1H, t, J=8.8 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 5-chloro-2-pyridyl ether (**29**)*
mp 91 °C, ^{1}H NMR δ: 4.26–4.30 (4H, m, $-(CH_2)_2-$), 6.54 (1H, d, J=8.8 Hz, pyridyl), 6.76 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.88 (1H, d, J=2.0 Hz, phenyl), 6.95 (1H, dd, J=7.8, 2.0 Hz, phenyl), 7.20 (1H, t, J=7.8 Hz, phenyl), 7.30 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 7.47 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 4-methyl-2-pyridyl ether (**30**)*
mp 96 °C. ^{1}H NMR δ: 2.18 (3H, s, $-CH_3$), 4.24–4.30 (4H, m, $-(CH_2)_2-$), 6.02 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 6.38 (1H, d, J=2.9 Hz, pyridyl), 6.74 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.86 (1H, d, J=2.0 Hz, phenyl), 6.92 (1H, d, J=8.8 Hz, pyridyl), 7.17 (1H, t, J=7.3 Hz, phenyl), 7.27 (1H, d, J=7.3 Hz, phenyl).

*1-(3-Chlorophenoxy)-2-(6-methyl-3-pyridyl)oxybutane (**9**)*

A mixture of 2-methyl-5-hydroxypyridine (3.00 g, 27 mmol), potassium carbonate (7.60 g, 55 mmol), and ethyl 2-bromobutyrate (6.43 g, 33 mmol) in dioxane (40 ml) was refluxed for 7 hr. The mixture was then allowed to cool to room temperature, and the product was purified in the same manner as that used for **1** to afford ethyl 2-(6-methyl-3-pyridyl)oxybutyrate (4.86 g, 79%). This ester was added dropwise to a suspension of lithium aluminum hydride (1.24 g, 33 mmol) in THF (40 ml) at 0 °C. After stirring for 3 hr at room temperature, the reaction mixture was quenched with water. After removal of the solvent under reduced pressure, the product was extracted three times with ethyl acetate. Concentration of the organic layer gave crude 2-(6-methyl-3-pyridyl)oxy-1-butanol (3.68 g, 100%). To a solution of this alcohol and triphenyl phosphine (8.56 g, 33 mmol) in THF (40 ml) at room temperature was added tetrabromomethane (10.82 g, 33 mmol). After stirring for 3 hr, the reaction mixture was diluted with hexane and filtered to remove triphenylphosphine oxide. After concentration of the filtrate, the residue was chromatographed on silica gel by eluting with hexane and ethyl acetate (1:1) to give 2.98 g (59%) of 1-bromo-2-(6-methyl-3-pyridyl)oxybutane (**II**). To a suspension of NaH (0.21 g, 5.1 mmol) in DMF (20 ml) was added dropwise 3-chlorophenol (0.53 g, 4.1 mmol) at 0 °C. After stirring for 30 minutes, to the mixture was added the above bromide (**II**) (0.80 g, 3.4 mmol) at room temperature. After stirring for 5 hr, the reaction mixture was quenched by adding water (30 ml), and then the resulting product was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane and ethyl acetate (3:1) to afford **9** (0.51 g, 53%) as an oil. ^1H NMR δ : 1.05 (3H, t, J=7.3 Hz, $-CH_2-CH_3$), 1.80–1.92 (2H, m, $-CH_2-CH_3$), 2.50 (3H, s, $-CH_3$), 4.04–4.15 (2H, m, $-CH-CH_2-O-$), 4.44–4.51 (1H, m, methine), 6.76 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.87–6.89 (2H, m, phenyl), 6.95 (1H, d, J=8.8 Hz, pyridyl), 7.02–7.10 (2H, m, phenyl and pyridyl), 8.25 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 6-ethyl-3-pyridyl ether (**21**)*

To a solution of conc. HCl (20 ml) and water (10 ml) was added furfurylamine (3.00 g, 31 mmol), and then acetaldehyde (1.83 g, 41 mmol) in water (6 ml) in such a way that the temperature did not exceed 0 °C. The above solution was added dropwise with stirring to refluxing 3 N HCl solution (32 ml). During addition the reaction mixture was kept under gentle reflux, while the addend was kept below 0 °C. After stirring for 10 minutes under reflux, the reaction mixture was allowed to cool to room temperature and then brought to pH 7.5–8.0 by addition of NaOH pellets. The product was extracted three times with ether, and the combined organic layer was dried over Na_2SO_4 and concentrated to yield 0.33 g (10%) of 2-ethyl-5-hydroxypyridine (**III**) (Clauson-Kaas and Meister, 1967). Compound **21** was prepared in the same manner as that used for compound **1** from 2-(3-chlorophenoxy)ethyl bromide and (**III**) in yield 40%, mp 57–58 °C. ^1H NMR δ : 1.28 (3H, t, J=7.3 Hz, $-CH_2-CH_3$), 2.78 (2H, q, J=7.3 Hz, $-CH_2-CH_3$), 4.32–4.35 (4H, m, $-(CH_2)_2-$), 6.84 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.96–6.98 (2H, m, phenyl), 7.09 (1H, d, J=8.8 Hz, pyridyl), 7.19–7.33 (2H, m, phenyl and pyridyl), 8.27 (1H, d, J=2.9 Hz, pyridyl).

*2-(3-Chlorophenoxy)ethyl 6-chloro-3-pyridyl ether (**22**)*

A mixture of 6-chloronicotinic acid (0.80 g, 5.1 mmol), potassium carbonate (1.19 g, 8.6 mmol) and iodoethane (0.95 g, 6.1 mmol) in acetonitrile (40 ml) was refluxed for 6 hr. The mixture was then cooled to room temperature, and the product was extracted with ether. Purification by column chromatography on silica gel eluting with hexane and ethyl acetate (1:1) to give 0.71 g (64%) of ethyl 6-chloronicotinate. This ester was added to a mixture of lithium aluminum hydride (0.16 g, 3.8 mmol) and diethylamine (0.56 g, 7.7 mmol) in pentane (20 ml) at room temperature (Cha and Kwon, 1987). After stirring for 1 hr, this reaction mixture was hydrolyzed with 2 N HCl solution (10 ml) by stirring vigorously for 6 hr at room temperature. The mixture was saturated with NaCl and the resulting aldehyde was extracted 5 times with ether. The combined organic layer was dried over Na_2SO_4 and concentrated to give 0.38 g (70%) of 2-chloro-5-formylpyridine (**IV**). To a solution of (**IV**) (0.38 g, 2.7 mmol) in dichloromethane (30 ml) at room temperature was added *m*-chloroperbenzoic acid (0.92 g, 5.3 mmol). The reaction mixture was stirred for 10 hr, and then quenched with 10% sodium thiosulfate solution (20 ml). To the mixture was added saturated $NaHCO_3$ solution (20 ml). After stirring for 10 minutes, the product was extracted with ether, and the organic layer was dried over Na_2SO_4 and concentrated to provide 0.42 g (100%) of 2-chloro-5-formyloxypyridine as a white solid. To a solution of this pyridyl formate (0.42 g, 2.7 mmol) in ethanol was added water (5 ml) and conc. HCl (10 ml) at room temperature. The reaction mixture was allowed to stir till all pyridyl formate disappeared on TLC. After neutralizing the reaction mixture with NaOH pellets, the product was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane and ethyl acetate (3:1) to provide 0.28 g (80%) of 2-chloro-5-hydroxypyridine (**V**). Compound **22** was prepared in the same manner as that used for compound **1** from 2-(3-chlorophenoxy)ethyl bromide and (**V**), as an oil. ^{1}H NMR δ: 4.30 (2H, t, J=7.3 Hz, $-CH_2-$), 4.67 (2H, t, J=7.3 Hz, $-CH_2-$), 6.83 (1H, dd, J=7.8, 2.0 Hz, phenyl), 6.92–6.98 (2H, m, phenyl), 7.21 (1H, t, J=7.8 Hz, phenyl), 7.54 (1H, dd, J=8.8, 2.9 Hz, pyridyl), 7.93 (1H, d, J=8.8 Hz, pyridyl), 8.01 (1H, d, J=2.9 Hz, pyridyl).

Biological evaluation

B. mori (Shunrei×Shougetsu strain) larvae were reared on artificial diets as previously reported (Yoshida *et al.*, 2000). Test compounds in acetone solution were applied topically to 72 hr-old 3 rd-instar and newly molted 4 th-instar larvae. Twenty larvae were used for each dose. The activity of compounds was evaluated by the induction of precocious metamorphosis: spinning a cocoon and subsequent pupation or formation of larval-pupal intermediates from the 4 th-instar (penultimate) larval period. There was no induction of precocious metamorphosis in control larvae treated only with the acetone solution.

RESULTS AND DISCUSSION

Synthesis

Synthetic methods of various pyridyl ethers are shown in Fig. 1. A variety of 6-methyl-3-pyridyl ethers were synthesized by the procedure shown in Fig. 1 (A). Alkylation of substituted phenol with 1,2-dibromoethane using sodium hydroxide as a base gave 2-(substituted phenoxy)ethyl bromide (**I**). Reaction of (**I**) with 2-methyl-5-hydroxypyridine in the presence of sodium hydride as a base provided 2-(substituted phenoxy)ethyl 6-methyl-3-pyridyl ethers (**1**, **4–7** and **10–19**). Similarly,

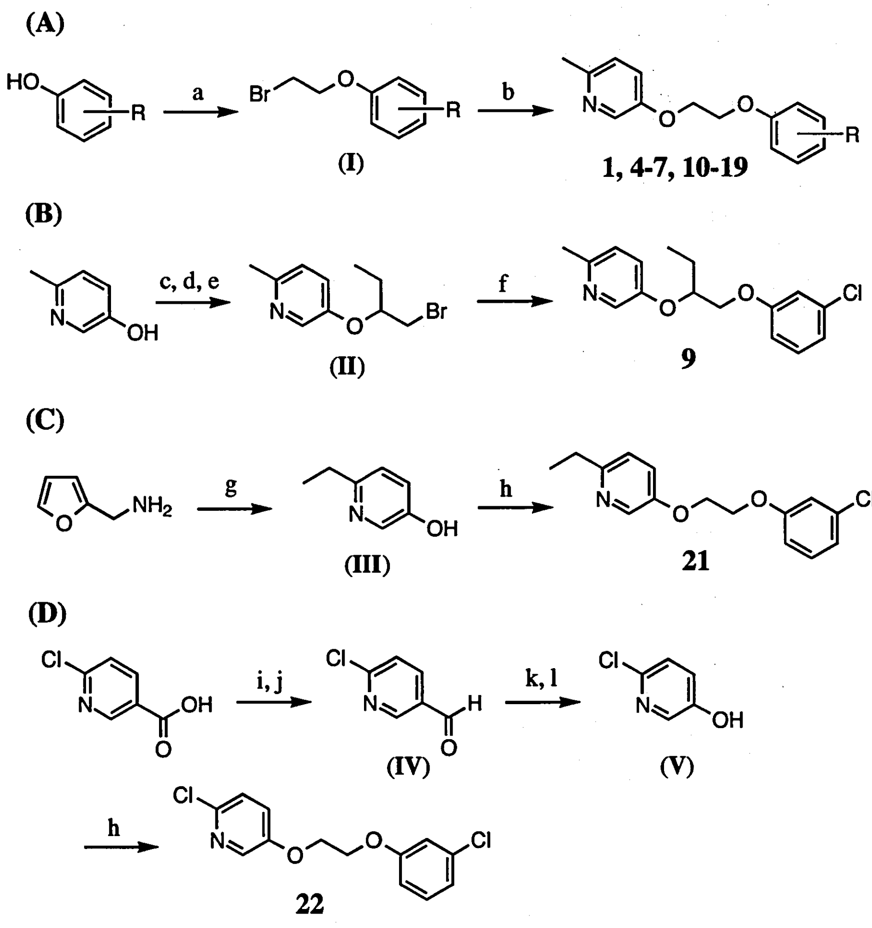


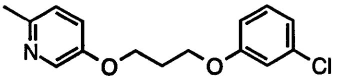
Fig. 1. Synthesis of pyridyl ethers.
Reagents: (a) 1,2-dibromoethane, NaOH, H_2O; (b) 2-methyl-5-hydroxypyridine, NaH, DMF; (c) ethyl 2-bromobutyrate, K_2CO_3, CH_3CN; (d) $LiAlH_4$, THF; (e) Ph_3P, CBr_4, THF; (f) 3-chlorophenol, NaH, DMF; (g) CH_3CHO, HCl, H_2O; (h) 2-(3-chlorophenoxy)ethyl bromide, NaH, DMF; (i) iodoethane, K_2CO_3, CH_3CN; (j) $LiAlH_4$, diethylamine, pentane; (k) *m*-chloroperbenzoic acid, CH_2Cl_2; (l) ethanol, H_2O, HCl

Compounds **20** and **23–30** were prepared by reaction of the corresponding 2-(3-chlorophenoxy)ethyl bromide with an appropriate hydroxypyridine. 1-(3-Chlorophenoxy)-2-(6-methyl-3-pyridyl)oxybutane (**9**) was prepared by the procedure outlined in Fig. 1 (B). Alkylation of 2-methyl-5-hydroxypyridine with ethyl 2-bromobutyrate followed by reduction with lithium aluminum hydride gave an alcohol, which was converted into the bromide (**II**) by treatment with triphenylphosphine and tetrabromomethane. Reaction of (**II**) with 3-chlorophenol using sodium hydride as a base gave compound **9**. Preparation of 2-(3-chlorophenoxy)ethyl 6-ethyl-3-pyridyl ether

(**21**) was accomplished by the procedure as shown in Fig. 1 (C). Treatment of furfurylamine with acetaldehyde in aqueous acidic solution afforded 2–ethyl–5–hydroxypyridine (**III**), which was treated with 2–(3–chlorophenoxy)ethyl bromide in the same manner as that used for compound **1** to provide compound **21**. Fig. 1 (D) represents the preparation of 2–(3–chlorophenoxy)ethyl 6–chloro–3–pyridyl ether (**22**). Conversion of 6–chloronicotinic acid into 2–chloro–5–formylpyridine (**IV**) was carried out by esterification with iodoethane using potassium carbonate as a base and subsequent reduction with lithium aluminum hydride and diethylamine. The Bayer–Villiger oxidation of (**IV**) with *m*–chloroperbenzoic acid followed by acidic hydrolysis provided 2–chloro–5–hyrdroxypyridine (**V**). Alkylation of (**V**) with 2–(3–chlorophenoxy)ethyl bromide using the same procedure employed in the synthesis of compound **1** afforded compound **22**.

Biological activity

As previously reported (Kim *et al.*, 2001), compound **1** showed precocious metamorphosis–inducing activity against 3 rd– and 4 th–instar larvae of the silkworm and was the most effective when applied to 72 hr–old 3 rd–instar larvae. Therefore, biological evaluation for various analogs was accomplished against 72 hr–old 3 rd–instar larvae. Table 1 shows precocious metamorphosis–inducing activity of some 6–methyl–3–pyridyl phenoxyethyl ethers with different substituents on the benzene ring. Compound **4**, which had exhibited weak activity against 24 hr–old 3 rd–instar larvae (Kim and Kuwano, 2001), did not induce precocious metamorphosis when applied to 72 hr–old 3 rd–instar larvae. The unsubstituted phenyl analog **5** did not show any activity at 100 μg. The 2–chlorophenyl analog **6** caused some larvae to undergo precocious pupation along with the prolongation of the larval period, but its activity was less than that of the 3–chlorophenyl analog **1**. The 4–chlorophenyl analog **7** had no activity.



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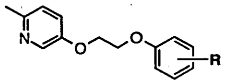
The activity was found to disappear with increasing length of the carbon chain between the two oxygen atoms (compound **8**). Compound **9** with a partial skeleton of ETB shown in Fig. 1 was inactive at 100 μg (data not shown). Thus, the ethyl ether moiety was important for induction of precocious metamorphosis.

Analogs with an electron–withdrawing group such as a fluoro (**10**), bromo (**11**) or trifluoromethyl (**12**) at the 3–position on the benzene ring showed some activity but not as high as compound **1**. The fact that the 3–methyl analog **13** induced precocious pupation suggested that the activity was not significantly influenced by the electron distribution on the benzene ring. Replacement of the 3–chloro substituent with an ethyl (**14**), methoxy (**15**) or isopropyl (**16**) group completely eliminated the activity at 100 μg. Although the 2– and 3–chloro analogs (**6** and **3**) induced precocious metamorphosis, the

Table 1. precocious metamorphosis-inducing activity of 6-methyl-3-pyridyl ethers against 72 hr-old 3 rd-instar larvae of *B. mori*



No.	R	Precocious metamorphosis (%) (100 μg/larva)
1	3-Cl	40
4	3-$CO_2C_2H_5$	0
5	H	0
6	2-Cl	15
7	4-Cl	0
10	3-F	25
11	3-Br	5
12	3-CF_3	15
13	3-CH_3	20
14	3-C_2H_5	0
15	3-OCH_3	0
16	3-*i*-C_3H_7	0
17	2,3-Cl	5
18	2,5-Cl	0
19	3,5-Cl	0

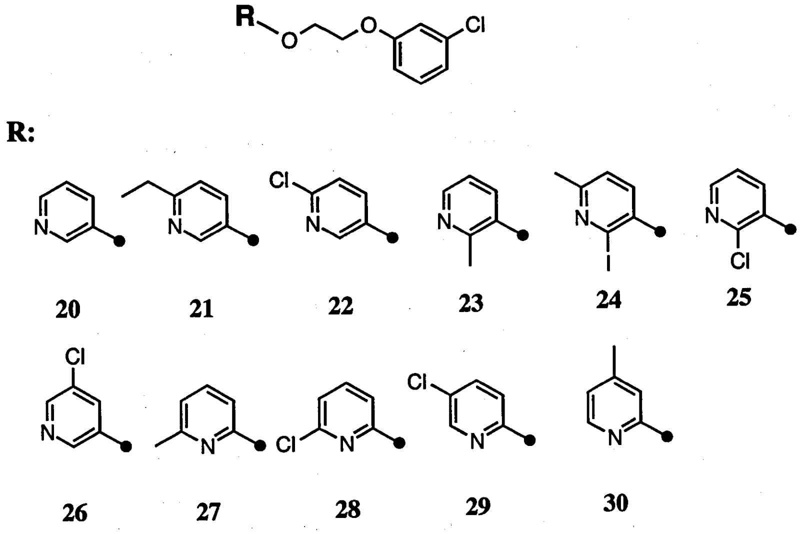


Fig. 2. Pyridyl ethers showing no precocious metamorphosis-inducing activity against 72 hr-old 3 rd-instar larvae of *B. mori* at 100 μg/larva.

additional introduction of a chlorine atom on the benzene ring (**17–19**) led to a decrease or elimination in activity.

Based on the above results, the 2–(3–chlorophenyl)ethyl moiety in compound **1** was fixed as a partial structure necessary for activity and a modification was made by replacing the 6–methyl–3–pyridyl portion with 3–pyridyl or various substituted pyridyl groups. None of the compounds **20–30** in Fig. 2 resulted in the induction of precocious pupation when applied to 72 hr–old 3 rd–instar larvae at 100 μg, indicating that the 6–methyl–3–pyridyl ether moiety was apparently essential for this activity. Thus, compound **1** was the most active of the analogs tested on the larvae of *B. mori*.

When 3 rd–instar larvae were treated with compound **1**, precocious metamorphosis always occurred in the 4 th (penultimate) larval stage. None of the treated 3 rd–instar larvae metamorphosed into precocious pupae in the same larval stage by a single topical application of compound **1**, which is similar to the effect of compound **2** (Kuwano *et al.*, 1998).

We have reported that precocious metamorphosis induced by 3–pyridine derivatives was always accompanied by the prolongation of the larval period (Yoshida *et al.*, 2000). The effect of compound **1** on the larval period is shown in Table 2. When applied to 72 hr–old 3 rd–instar larvae, there was no difference in the 3 rd larval period between controls and treated larvae. Extreme delay was observed in the 4 th larvae which were destined to undergo precocious pupation by treating compound **1**. It is well–known that an application of JH agonists to last larval instars prolongs the larval period to form supernumerary molting larvae or permanent larvae (Hatakoshi *et al.*, 1986). We examined the effect of the 2–pyridyl ether pyriproxyfen, a JH agonist, on larval growth when applied to 72 hr–old 3 rd–instar larvae. Although it prolonged the duration of 4 th instar one to two days, eventually all of the treated larvae molted to 5th–instar larvae (Table 2). It is likely that extraordinary prolongation of the 4 th larval (penultimate) period is responsible for the induction of precocious pupation.

Precocious metamorphosis induced by compound **1** was completely prevented by an application of 10 μg of methoprene, a JH agonist, suggesting that compound **1** temporarily depress the JH titer in the larval hemolymph to induce precocious pupation. Although the mode of action of compound **1** has not been studied yet, this series of

Table 2. Effects of compound 1 and pyriproxyfen on 72 hr–old 3 rd–instar larvae of *B. mori*

Compound (100 μg/larva)	Larval period (days ± SD)		Precocious metamorphosis (%)
	3 rd instar	4 th instar	
1	3.9 ± 0.3	5.6 ± 0.7 (9.4 ± 0.7)[a]	40
Pyriproxyfen	4.1 ± 0.2	7.0 ± 0.7[a]	0
Control	4.3 ± 0.4	5.2 ± 0.4	0

[a] Significant difference from the control value ($p < 0.01$). Figure in parenthesis shows the duration of 4 th–instar larvae which metamorphosed into precocious pupae.

6–methyl–3–pyridines is worthy of further investigation for development of new anti–JH agents.

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