Synthesis and Insect Growth Regulatory Activity of Alkoxy-Substituted Benzaldoxime Ethers

H. Chowdhury,[†] V. S. Saxena,[‡] and S. Walia*[,†]

Divisions of Agricultural Chemicals and Entomology, Indian Agricultural Research Institute, New Delhi 110 012, India

Alkoxy-substituted benzaldoxime ethers, namely (i) 3-methoxy-4-ethoxybenzaldoxime N−O−alkyl ethers, (ii) 3,4-dimethoxybenzaldoxime N−O−alkyl ethers, and (iii) 3,4-methylenedioxybenzaldoxime N−O−alkyl ethers, have been synthesized and evaluated for their insect growth regulatory activity against fifth-instar nymphs of the desert locust *Schistocerca gregaria* F. When injected into insect hemolymph at the lowest dose level of 3 μg/nymph, 3,4-methylenedioxybenzaldoxime N−O−methyl ether and 3,4-methylenedioxybenzaldoxime N−O−isopropyl ether showed 40 and 50% growth deformities respectively. On topical application (at 20 μg/nymph) 3-methoxy-4-ethoxybenzaldoxime N−O−methyl ether inflicted 100% abnormalties in insect growth. Structure−activity relationship studies revealed that maximum activity was associated with compounds having three carbons in the oxime ether moiety.

Keywords: *Insect growth regulators; oxime ethers; Schistocerca gregaria*

Biosynthesis and release of insect growth hormones such as brain hormones (BHs), juvenile hormones (JHs), and molting hormones (MHs) govern the growth, molting, and development of insects (Reynolds and Truman, 1980; Chippendale, 1977; Goodman, 1990; Ridiford, 1994). Because of the regulatory functions of insect juvenile hormones in insect embryogenesis, larval growth, metamorphosis, reproduction, hibernation, migration, and metabolism, compounds mimicking or antagonizing the function of juvenile hormones are considered an important group of third-generation insecticides. Being generally environmentally benign and possessing relatively selective mode of action, such compounds are considered safer alternatives to conventional highly persistent and toxic insecticides (Miyamoto et al., 1993). Among the various groups of insect growth regulators (IGRs) having diverse structural features, interest in oxime ethers has grown considerably in recent years because of their overall impact on the insect endocrine system. Several oxime ethers have been synthesized previously and evaluated for their IGR activity (Hayashi et al., 1990, 1991a,b; Nakayama et al., 1985; Niwa et al., 1988; Ohsumi et al., 1985), insecticidal activity (Bull et al., 1980; Nanjyo et al., 1980), and insecticide synergistic activity (Walia et al., 1985). In this paper we report the synthesis, IGR activity, and structure−activity relationships of three series of oxime ethers, namely (i) 3-methoxy-4-ethoxybenzaldoxime N−O−alkyl ethers, (ii) 3,4-dimethoxybenzaldoxime N−O−alkyl ethers, and (iii) 3,4-methylenedioxybenzaldoxime N−O−alkyl ethers against the desert locust *Schistocerca gregaria* (Forsk).

MATERIALS AND METHODS

Chemicals and Reagents. Vanillin, veratraldehyde, alkyl bromides, and acrylonitrile required for the study were procured from S. D. Fine Chem Ltd., Mumbai, India, and used without further purification. Piperonal was obtained from Aldrich Chemical Co. The organic solvents used in chromatography, crystallization, and organic syntheses were of reagent grade.

Chromatography and Spectroscopy. Thin-layer chromatography (TLC) was performed on silica gel G plates preactivated at 100 °C. The plates were developed in hexane/acetone (75:25) and visualized by either iodine vapors or spraying with 2,4-dinitrophenylhydrazine solution. Silica gel (60−120) mesh was used for column chromatography using hexane and hexane/acetone gradient. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard model 5890A gas chromatograph equipped with a flame ionization detector (FID) and fitted with a glass column packed with 3% OV-225 on Chromosorb W.

The ^{1}H NMR spectra were recorded on a Varian EM-360, 60-MHz instrument. Samples were dissolved in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard. Chemical shifts are reported in δ values relative to TMS. Infrared (IR) spectra were scanned on a Digilab infrared spectrophotometer in either Nujol or KBr disk. The mass spectra (MS) were recorded on a DS-90 mass spectrometer at 70 eV using electron impact ionization.

Elemental Analysis. C, H, and N analysis was done on a Perkin-Elmer 2400 C H N elemental autoanalyzer by Dumas total combustion process using acetonitrile as standard. The observed values were within ±0.5% of the theoretical values.

Synthesis of Substituted Benzaldoximes. Equimolar quantities of hydroxylamine hydrochloride and substituted benzaldehydes such as 3-methoxy-4-ethoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, and 3,4-methylenedioxybenzaldehyde (piperonal) were refluxed in ethanol for 3 h in the presence of anhydrous potassium carbonate. After completion of the reaction (TLC), inorganic salts (KCl and K_2CO_3) were filtered off and the solvent was removed by distillation under reduced pressure to give a viscous mass which crystallized from ethanol as white powder. 3-Methoxy-4-ethoxybenzaldehyde was prepared by refluxing solution of vanillin and ethyl bromide in dry acetone containing anhydrous potassium carbonate. These compounds were characterized by ^{1}H NMR spectroscopy.

3-Methoxy-4-ethoxybenzaldoxime N−O−Alkyl Ethers. A solution of 3-methoxy-4-ethoxybenzaldoxime (3.9 g; 0.02 mol)

* Author to whom correspondence should be addressed.
[†] Division of Agricultural Chemicals.
[‡] Division of Entomology.

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in dry acetone (200 mL) containing anhydrous potassium carbonate (10 g) was refluxed with appropriate alkyl halide (0.025 M) for 10 h. After completion of the reaction (TLC), the solid potassium carbonate was filtered out, water (200 mL) added, and the reaction mixture neutralized with dilute HCl (pH 7.0). The aqueous layer was then extracted with ethyl acetate (2 × 100 mL), and the combined extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was then distilled off and the concentrated material subjected to column chromatography over silica gel using hexane/benzene (1:1) as eluent to furnish oxime ethers either in crystalline form or as viscous liquid.

*3-Methoxy-4-ethoxybenzaldoxime N−O−methyl ether (**I**):* yield 3.3 g (79%); R_f 0.66; ^{1}H NMR ($CDCl_3$) δ 1.4 (t, 3H, $-OCH_2C\mathbf{H_3}$, J = 7 Hz), 3.8 (s, 3H, $-OC\mathbf{H_3}$), 3.95 (s, 3H, $-NOC\mathbf{H_3}$), 4.0 (q, 2H, $-OC\mathbf{H_2}CH_3$, J = 7 Hz), 6.75 (d, 1H, J = 8 Hz), 6.93 (dd, 1H, J = 8 and 1.5 Hz), 7.25 (d, 1H, J = 1.5 Hz), 8.0 (s, 1H, −CH═N−). Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.16; H, 7.18; O, 23.0; N, 6.70. Found: C, 63.0; H, 7.17; O, 23.10; N, 6.71.

*3-Methoxy-4-ethoxybenzaldoxime N−O−ethyl ether (**II**):* yield 3.7 g (83%); R_f 0.71; mp 42 °C; IR (ν Nujol, cm^{-1}) 720, 810, 945, 1010, 1090, 1140, 1245, 1450, 1500, 1575 1600; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, $-NOCH_2C\mathbf{H_3}$, J = 7 Hz), 1.40 (t, 3H, $Ar-OCH_2C\mathbf{H_3}$, J = 7 Hz), 3.85 (s, 3H, $-OCH_3$), 4.15 (q, 2H, $-NOC\mathbf{H_2}CH_3$, J = 7 Hz), 4.20 (q, 2H, $Ar-OC\mathbf{H_2}CH_3$, J = 7 Hz), 6.75 (d, 1H, J = 8 Hz), 7.02 (dd, 1H, J = 8 and 1.5 Hz), 7.25 (d, 1H, J = 1.5 Hz), 8.0 (s, 1H, −CH═N−); MS 223 (M$^+$, 100%), 209 (27.6%), 195 (58.6%), 178 (30%), 150 (46%), 134, 124, 106, 79, 77. Anal. Calcd for $C_{12}H_{17}O_3N$: C, 64.57; H, 7.62; O, 21.52; N, 6.28. Found: C, 64.63; H, 7.60; O, 21.51; N, 6.20%.

*3-Methoxy-4-ethoxybenzaldoxime N−O−n-propyl ether (**III**):* yield 3.9 g (82.3%); R_f 0.74; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, $-NOCH_2CH_2C\mathbf{H_3}$, J = 7 Hz), 1.40 (t, 3H, $Ar-OCH_2C\mathbf{H_3}$, J = 7 Hz), 1.60 (m, 2H, $-NOCH_2C\mathbf{H_2}CH_3$), 3.76 (s, 3H, $-OCH_3$), 4.00 (t, 2H, $-NOC\mathbf{H_2}CH_2CH_3$, J = 7 Hz), 4.15 (q, 2H, $Ar-OC\mathbf{H_2}CH_3$, J = 7 Hz), 6.75 (d, 1H, J = 8 Hz), 6.97 (dd, 1H, J = 8 and 1.5 Hz), 7.25 (d, 1H, J =1.5 Hz), 7.93 (s, 1H, −CH═N−). Anal. Calcd for $C_{13}H_{19}O_3N$: C, 65.8; H, 8.02; O, 20.25; N, 5.91. Found; C, 65.70; H, 8.03; O, 20.26; N, 6.0.

*3-Methoxy-4-ethoxybenzaldoxime N−O−isopropyl ether (**IV**):* yield 4.1 g (86.5%); R_f 0.73; mp 49−50 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 [d, 6H, $-CH(C\mathbf{H_3})_2$, J = 6 Hz], 1.40 (t, 3H, $Ar-OCH_2C\mathbf{H_3}$, J = 7 Hz), 3.80 (s, 3H, $-OCH_3$), 4.0 (q, 2H $-OC\mathbf{H_2}CH_3$, J = 7 Hz), 4.45 [m, 1H, $-NOC\mathbf{H}(CH_3)_2$], 6.75 (d, 1H, J = 8 Hz), 6.98 (dd, 1H, J = 8 and 1.5 Hz), 7.23 (d, 1H, J = 1.5 Hz), 7.96 (s, 1H, −CH═N−). Anal. Calcd for $C_{13}H_{19}O_3N$: C, 65.82; H, 8.02; O, 20.25; N, 5.91. Found: C, 65.80; H, 8.03; O, 20.27; N, 5.89.

*3-Methoxy-4-ethoxybenzaldoxime N−O−n-butyl ether (**V**):* yield 4.0 g (79.7%); R_f 0.75; IR (ν Nujol, cm^{-1}) 675, 840, 990, 1050 1235, 1265, 1460, 1500, 1575, 1600; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, $-NOCH_2CH_2CH_2C\mathbf{H_3}$, J = 7 Hz), 1.45 (t, 3H, $-ArOCH_2C\mathbf{H_3}$, J = 7 Hz), 1.2−1.9 [m, 4H, $-NOCH_2(C\mathbf{H_2})_2CH_3$], 3.83 (s, 3H, $-OCH_3$), 4.0 (t, 2H, $NOC\mathbf{H_2}CH_2CH_2CH_3$, J = 7 Hz), 4.15 (q, 2H, $-ArOC\mathbf{H_2}CH_3$, J = 7 Hz), 6.70 (d, 1H, J = 8 Hz), 6.97 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 1.5 Hz), 7.90 (s, 1H, −CH═N−); MS 251 (M$^+$, 100%), 220 (48%), 206 (69%), 195 (45%), 192 (31%), 179 (89.6%), 167 (54%), 150 (93%), 124, 109, 79, 77. Anal. Calcd for $C_{14}H_{21}O_3N$: C, 66.93; H, 8.37; O, 19.12; N, 5.58. Found: C, 66.94, H, 8.35; O, 19.13; N, 5.57.

*3-Methoxy-4-ethoxybenzaldoxime N−O−n-pentyl ether (**VI**):* yield, 4.5 g (84.9%); R_f 0.77; mp 40 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 [t, 3H, $-NOCH_2(CH_2)_3C\mathbf{H_3}$, J = 7 Hz], 1.40 (t, 3H, $Ar-OCH_2C\mathbf{H_3}$, J = 7 Hz), 1.20−1.90 [m, 6H, $-NOCH_2(C\mathbf{H_2})_3CH_3$], 3.80 (s, 3H, $-OCH_3$), 3.94 [t, 2H, $-NOC\mathbf{H_2}(CH_2)_3CH_3$, J = 7 Hz], 4.0 (q, 2H, $Ar-OC\mathbf{H_2}CH_3$), 6.70, (d, 1H, J = 8 Hz), 6.91 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 1.5 Hz), 7.93 (s, 1H, −CH═N−). Anal. Calcd for $C_{15}H_{23}O_3N$: C, 67.92; H, 8.68; O, 18.11; N, 5.28. Found: C, 67.90; H, 8.69; O, 18.12; N, 5.27.

*3- Methoxy-4-ethoxybenzaldoxime N−O−Cyanoethyl Ether (**VII**).* A solution of 3-methoxy-4-ethoxybenzaldoxime (0.02 M, 3.90 g) in dimethylformamide (10 mL) was stirred by a magnetic stirrer along with acrylonitrile (0.025 M, 1.35 g) at ambient temperature. While stirring, sodium hydroxide (15%, 5 mL) was added to the mixture in 1-mL portions. After completion of the reaction (TLC), water (50 mL) was added and the mixture neutralized with dilute hydrochloric acid (pH 7.0). The precipitated compound was filtered and crystallized from methanol as a brown solid: yield, 4.0 g, 80.64%; R_f 0.45; mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, $Ar-OCH_2C\mathbf{H_3}$, J = 7 Hz), 3.78 (t, 2H, $-OCH_2C\mathbf{H_2}CN$, J = 6 Hz), 3.85(s, 3H, $-OCH_3$), 4.20 (q, 2H, $Ar-OC\mathbf{H_2}CH_3$, J = 7 Hz), 4.35 (t, 2H, $-NOC\mathbf{H_2}CH_2CN$, J = 6 Hz), 6.75 (d, 1H, J = 8 Hz), 6.98 (dd, 1H, J = 8 and 1.5 Hz), 7.25 (d, 1H, J = 1.5 Hz), 8.00 (s, 1H, −CH═N−). Anal. Calcd for $C_{13}H_{16}O_3N_2$: C, 62.90; H, 6.45; O, 19.35; N, 11.29. Found: C, 62.80; H, 6.50; O, 19.39; N, 11.30%.

*3,4-Dimethoxybenzaldoxime N−O−methyl ether (**VIII**):* yield 3.5 g (89.7%); R_f 0.55; mp 50 °C; ^{1}H NMR ($CDCl_3$) δ 3.85, 3.88 (s, 2 × $-OCH_3$), 3.93 (s, 3H, $-NOCH_3$), 6.83 (d, 1H, J = 8 Hz), 7.02 (dd, 1H, J = 8 and 1.5 Hz), 7.29 (d, 1H, J = 2 Hz), 8.05 (s, 1H, −CH═N−). Anal. Calcd for $C_{10}H_{13}O_3N$: C, 61.54; H, 6.67; O, 24.61; N, 7.18. Found: C, 61.14; H, 6.36; O, 25.01; N, 7.49.

*3,4-Dimethoxybenzaldoxime N−O−ethyl ether (**IX**):* yield 3.5 g (83.7%); R_f 0.60; mp 49−51 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, $OCH_2C\mathbf{H_3}$, J = 6 Hz), 3.88, 3.90 (s, 2 × $-OCH_3$), 4.27 (q, 2H, $-OC\mathbf{H_2}CH_3$, J = 6 Hz), 6.85 (d, 1H, J = 8 Hz), 7.13 (dd, 1H, J = 8 and 1.5 Hz), 7.35 (d, 1H, J = 2 Hz), 8.10 (s, 1H, −CH═N−). Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.15, H, 7.18; O, 22.96; N, 6.70. Found; C, 63.25; H, 7.04; O, 22.98; N, 6.71.

*3,4-Dimethoxybenzaldoxime N−O−n-propyl ether (**X**):* yield 3.6 g (80.7%); R_f 0.64; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, $-OCH_2CH_2C\mathbf{H_3}$, J = 6 Hz), 1.70 (m, 2H, $-OCH_2C\mathbf{H_2}CH_3$), 3.80, 3.78 (s, 2 × $-OCH_3$), 4.10 (t, 2H, $-OC\mathbf{H_2}CH_2CH_3$, J = 6 Hz), 6.73 (s, 1 H, J = 8 Hz), 6.98 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (s, 1H, J = 2 Hz), 7.93 (s, 1H, −CH═N−). Anal. Calcd for $C_{12}H_{17}O_3N$: C, 64.57; H, 7.62; O, 21.52; N, 6.28. Found: C, 63.9; H, 7.69; O, 21.92; N, 6.48.

*3,4-Dimethoxybenzaldoxime N−O−isopropyl ether (**XI**):* yield 3.4 g (76.2%); R_f 0.64; IR(ν Nujol, cm^{-1}) 1810, 975, 1200, 1050, 1160, 1280, 1500, 1600; ^{1}H NMR ($CDCl_3$) δ 1.25 [d, 6H, $-OCH(C\mathbf{H_3})_2$, J = 6 Hz], 3.80, 3.79 (s, 2 × OCH_3), 4.40 [m, 1H, $-C\mathbf{H}(CH_3)_2$], 6.72 (d, 1H, J = 8 Hz), 6.98 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (s, 1H, J = 2 Hz), 7.90 (s, 1H, −CH═N−); MS 223 (M$^+$, 100%), 181 (75%), 165 (57.5%), 150 (32.2%), 138 (66.7%), 120, 107, 92, 79, 77. Anal. Calcd for $C_{12}H_{17}O_3N$: C, 64.57; H, 7.62; O, 21.52; N, 6.28. Found: C, 64.78; H, 7.50; O, 21.41; N, 6.29.

*3,4-Dimethoxybenzaldoxime N−O−n-butyl ether (**XII**):* yield 3.9 g (82.3%); R_f 0.65; ^{1}H NMR ($CDCl_3$) δ 0.95 [t, 3H, $-O(CH_2)_3C\mathbf{H_3}$, J = 6 Hz], 1.25−1.90 (m, 4H, $-OCH_2C\mathbf{H_2}C\mathbf{H_2}CH_3$), 3.70, 3.75 (s, 2 × $-OCH_3$), 4.10 (t, 2H, $-OC\mathbf{H_2}CH_2CH_2CH_3$, J = 6 Hz), 6.70 (d 1H, J = 8 Hz), 6.93 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 2 Hz), 7.93 (s, 1H, −CH═N−). Anal. Calcd for $C_{13}H_{19}O_3N$: C, 65.82; H, 8.02; O, 20.25; N, 5.90. Found: C, 65.53; H, 8,24; O, 20.21; N, 6.01.

*3,4-Dimethoxybenzaldoxime N−O−pentyl ether (**XIII**):* yield 4.4 g (87.6%); R_f 0.68; ^{1}H NMR ($CDCl_3$) δ 0.93 [t, 3H $-O(CH_2)_4C\mathbf{H_3}$, J = 6 Hz], 1.20−1.88 [m, 6H, $-OCH_2(C\mathbf{H_2})_3CH_3$], 3.78, 3.80 (s, 2 × $-OCH_3$), 4.10 [t, 2H, $-OC\mathbf{H_2}(CH_2)_3CH_3$, J = 6 Hz], 6.70(d, 1H, J = 8 Hz), 6.98 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 2 Hz), 7.90 (s, 1H, −CH═N−). Anal. Calcd for $C_{14}H_{21}O_3N$: C, 66.93; H, 8.37; O, 19.12; N, 5.58. Found: C, 66.91; H, 8.39; O, 19.13; N, 5.56.

*3,4-Dimethoxybenzaldoxime N−O−cyanoethyl ether (**XIV**):* yield 4.0 g (85.5%); R_f 0.35; mp 85 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (t, 2H, $-OCH_2C\mathbf{H_2}CN$, J = 6 Hz), 3.90 (s, 2 × OCH_3), 4.35 (t, 2H, $-OC\mathbf{H_2}CH_2CN$, J = 6 Hz), 6.90 (d, 1H, J = 8 Hz), 7.13 (dd, 1H, J = 8 and 1.5 Hz), 7.30 (d, 1H, J = 2 Hz), 8.10 (s, 1H, −CH═N−); MS 234 (M$^+$, 100%), 219 (34.5%), 203 (31%), 181 (38%), 164 (75%), 137 (71.3%), 122, 107, 92, 79, 77. Anal. Calcd for $C_{12}H_{14}O_3N_2$: C, 61.53; H, 5.98; O, 20.51; N, 11.97. Found: C, 61.90; H, 6.01; O, 20.20; N, 11.83.

*3,4-Methylenedioxybenzaldoxime N−O−methyl ether (**XV**):* yield 2.9 g (76.7%); R_f 0.75; mp 37 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H, $-OCH_3$), 5.90 (s, 2H, $-OCH_2O-$), 6.75 (d, 1H, J = 8 Hz), 6.99 (dd, 1H, J = 8 and 1.5 Hz), 7.22 (d, 1H, J = 2 Hz), 7.92 (s, 1H, −CH═N−); MS 179 (M$^+$ 100%), 164 (6%) 148

(60%), 134 (46%), 121 (65.5%), 107, 91. Anal. Calcd for $C_9H_9O_3N$: C, 60.33; H, 5.03; O, 26.81; N, 7.82. Found: C, 60.40; H, 5.10; O, 26.40; N, 8.09.

*3,4-Methylenedioxybenzaldoxime N−O−ethyl ether (**XVI**):* yield, 3.3 g (85.5%); R_f 0.77; ^{1}H NMR ($CDCl_3$) δ 0.95 [t, 3H, $-OCH_2C\mathbf{H_3}$, J = 6 Hz), 4.20 (q, 2H, $-OC\mathbf{H_2}CH_3$), 5.90 (s, 2H, $-OCH_2O-$), 6.73 (d, 1H, J = 8 Hz), 6.89 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 2 Hz), 7.90 (s,1H, −CH=N−). Anal. Calcd for $C_{10}H_{11}O_3N$: C, 62.18; H, 5.70; O, 24.87; N, 7.25. Found: C, 62.03; H, 5.81; O, 24.89; N, 7.26.

*3,4-Methylenedioxybenzaldoxime N−O−n-propyl ether (**XVII**):* yield, 3.5 g (84.5%); R_f 0.79; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, $-OCH_2CH_2C\mathbf{H_3}$, J = 6 Hz), 1.70 (m, 2H, $-OCH_2C\mathbf{H_2}CH_3$), 4.05 (t, 2H, -$OC\mathbf{H_2}CH_2CH_3$, J = 6 Hz), 5.90 (s, 2H, $-OCH_2O-$), 6.65 (d, 1H, J = 8 Hz), 6.93 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 2 Hz), 7.86 (s, 1H, CH=N−). Anal. Calcd for $C_{11}H_{13}O_3N$: C, 63.77; H, 6.28; O, 23.19; N, 6.76. Found: C, 63.80; H, 6.25; O, 23.20; N, 6.74.

*3,4-Methylenedioxybenzaldoxime N−O−isopropyl ether (**XVIII**):* yield, 3.6 g (87.0%); R_f 0.77; ^{1}H NMR ($CDCl_3$) δ 1.24 [d, 6H, $-OCH(C\mathbf{H_3})_2$, J = 6 Hz], 4.40 [m, 1H, $-OC\mathbf{H}(CH_3)_2$], 5.92 (s, 2H, $-OCH_2O-$), 6.70 (d, 1H, J = 8 Hz), 6.93 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 2 Hz), 7.90 (s, 1H, −CH=N−); MS 207 (M^+, 100%), 165 (88.5%), 148 (62%), 138 (63%), 122 (75%), 107, 91, 76. Anal. Calcd for $C_{11}H_{13}O_3N$: C, 63.77; H, 6.28; O, 23.19; N, 6.76. Found: C, 63.47; H, 6.29; O, 23.02; N, 7.21.

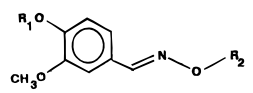
*3,4-Methylenedioxybenzaldoxime N−O−n-butyl ether (**XIX**):* yield, 3.8 g (86.0%); R_f 0.97; mp 42−43 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, $N-OCH_2CH_2CH_2\mathbf{CH_3}$, J = 6 Hz), 1.10−1.80 [m, 4H, $OCH_2(C\mathbf{H_2})_2CH_3$], 4.10 (t, 2H, $-OC\mathbf{H_2}CH_2CH_2CH_3$, J = 6 Hz), 5.93 (s, 2H, $-OCH_2O-$), 6.73 (d, 1H, J = 8 Hz), 6.93 (dd, 1H, J = 8 and 1.5 Hz), 7.21 (d, 1H, J = 2 Hz), 7.96 (s, 1H, −CH=N−). Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.82; H, 8.02; O, 20.25; N, 5.90. Found: C, 66.02; H, 8.15; O, 20.15; N, 5.79.

*3,4-Methylenedioxybenzaldoxime N−O−n-pentyl ether (**XX**):* yield 3.9 g (83.0%); R_f 0.98; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, $-OCH_2CH_2CH_2CH_2C\mathbf{H_3}$, J = 6 Hz), 1.20−1.80 [m, 6H, $-OCH_2(C\mathbf{H_2})_3CH_3$,], 4.10 [t, 2H, $-OC\mathbf{H_2}(CH_2)_3CH_3$, J = 6 Hz], 5.91 (s, 2H, $-OCH_2O-$), 6.72 (d, 1H, J = 8 Hz), 6.93 (dd, 1H, J = 8 and 1.5 Hz), 7.20 (d, 1H, J = 2 Hz), 7.90 (s, 1H, −CH=N−). Anal. Calcd for $C_{13}H_{17}O_3N$: C, 66.38; H, 7.23; O, 20.43; N, 5.96. Found: C, 66.32; H, 7.30; O, 20.41; N, 5.92.

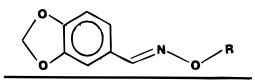
*3,4-Methylenedioxybenzaldoxime N−O−cyanoethyl ether (**XXI**):* yield 3.7 g (85.0%); R_f 0.30; mp 82 °C; ^{1}H NMR ($CDCl_3$) δ 2.72 (t, 2H, $-OCH_2C\mathbf{H_2}CN$, J = 6 Hz), 4.30 (t, 2H, $-OC\mathbf{H_2}$-CH_2CN, J = 6 Hz), 5.98 (s, 2H, $-OCH_2O-$), 6.71 (d, 1H, J = 8 Hz), 6.93 (dd, 1H, J = 8 and 1.5 Hz), 7.12 (d, 1H, J = 2 Hz), 7.96 (s, 1H, −CH=N). Anal. Calcd for $C_{11}H_{10}O_3N_2$: C, 60.55; H, 4.59; O, 22.01; N, 12.84. Found: C, 61.0; H, 4.48; O, 22.0; N, 12.51.

Lipophilicity of Test Compounds. Lipophilicity of the test compounds was determined by finding out the R_f values on reversed-phase TLC and then calculating the R_M values by using the equation $R_M = \log(1/R_f - 1)$ (Boyce and Milborrow, 1965). Silica gel plates, after activation for 2 h at 100 °C, were coated with paraffin in hexane (10:90). The paraffin-coated plates were then spotted with the test compounds and developed in an acetone/water (60:40) solvent system. The spots were visualized by spraying with 2,4-dinitrophenylhydrazine reagent solution. R_f values were measured to calculate R_M values. The experiment was repeated thrice, and the mean of three replicates was used for derivation of R_M values.

Bioassay. A stock culture of *S. gregaria* (Forsk) (family, Acarididae; order, Orthoptera) was maintained in the laboratory on cabbage and maize leaves (Mehrotra et al., 1966) at a temperature ranging from 30 to 40 °C. Three concentrations of oxime ethers (10, 5, and 3 μg in 5 μL of ethanol) were injected through the intersegmental membrane into the abdomen of each nymph by a hypodermic syringe fitted to a microapplicator (Burkard). The IGR activity of the test compounds was compared with that of the standard reference buprofezin (Applaud,) under similar test concentrations. An equal number of hoppers injected with only ethanol served as control. An untreated control for each treatment was simultaneously maintained.



S. No.	R_1	R_2
I	C_2H_5	CH_3
II	C_2H_5	C_2H_5
III	C_2H_5	$C_3H_{7(n)}$
IV	C_2H_5	$C_3H_{7(i)}$
V	C_2H_5	$C_4H_{9(n)}$
VI	C_2H_5	$C_5H_{11(n)}$
VII	C_2H_5	CH_2CH_2CN
VIII	CH_3	CH_3
IX	CH_3	C_2H_5
X	CH_3	$C_3H_{7(n)}$
XI	CH_3	$C_3H_{7(i)}$
XII	CH_3	$C_4H_{9(n)}$
XIII	CH_3	$C_5H_{11(n)}$
XIV	CH_3	CH_2CH_2CN



S.No.	R
XV	CH_3
XVI	C_2H_5
XVII	$C_3H_{7(n)}$
XVIII	$C_3H_{7(i)}$
XIX	$C_4H_{9(n)}$
XX	$C_5H_{11(n)}$
XXI	CH_2CH_2CN

Figure 1. Generic structures of substituted benzaldoxime N−O−alkyl ethers.

Similarly, 20 and 5 μg of the test compound in 5 μL of acetone was topically applied on the ventral side of individual hoppers by the same microapplicator. An equal number of hoppers treated topically with only acetone (5 mL) served as control. After treatment, insects were kept in glass jars (30 cm × 20 cm) with sufficient food (cabbage leaf) for daily observation. Insects were kept at 30 ± 1 °C under 12-h dark and 12-h light conditions.

RESULTS AND DISCUSSION

3-Methoxy-4-ethoxybenzaldoxime, 3,4-dimethoxybenzaldoxime, and 3,4-methylenedioxybenzaldoxime needed for the preparation of oxime ethers were obtained by reacting corresponding substituted benzaldehydes with hydroxylamine hydrochloride. Their identities were confirmed by ^{1}H NMR spectra. The oximes are usually a 1:1 mixture of cis and trans isomers and are inseparable by conventional chromatographic techniques. The oximes were then reacted with alkyl halides/acrylonitrile to furnish oxime ethers, which were bioassayed as mixtures of both isomers.

Table 1. IGR Activity of Oxime Ethers on Fifth-Instar Nymphs of *S. gregaria* When Injected at 10, 5, and 3 μg/Nymph ($n = 10$, $R = 2$)

test chemical	R_m value	nymphs dead (%)	nymph−adult intermediates (%)	abnormal adults (%)	total abnormality (%)	normal adults survived (%)	normal adults dead (%)
I	−0.445	20[a]		20	20	40	20
II	−0.292	20/10	40/20	20/10	60/30	20/60	
III	−0.151	30		20	20	30	20
IV	−0.140	20	20	10	30	30	20
V	−0.036	20/10/0	40/10/20	20/40/20	60/50/40	20/40/60	
VI	0.214	20	20		20	60	
VII	−0.632	20		20	20	60	
VIII	−0.613	0/10	40/0	0/30	40/30	60/60	
IX	−0.463	20/20/10	60/40/20	0/0/20	60/40/40	20/30/50	0/10/0
X	−0.295	0/0/0	0/50/0	60/10/40	60/60/40	40/40/50	0/0/10
XI	−0.313	20/20/0	20/40/20	40/10/20	60/50/40	20/30/50	0/0/0
XII	−0.098	20		20	20	60	
XIII	−0.074		20	20	40	60	
XIV	−0.935						
XV	−0.309	0/10/10	40/30/0	60/40/40	100/70/40	0/10/40	0/10/10
XVI	−0.131	20/20/10	20/30/20	60/20/10	80/50/30	0/30/60	0/0/0
XVII	0.064	20/20	0/20	40/0	40/20	40/60	0/0
XVIII	0.0	10/10/10	60/60/10	20/10/40	80/70/50	10/20/30	0/0/10
XIX	0.265					100	
XX	0.474					100	
XXI	−0.673			20	20	80	
Applaud		10/10/10	40/30/10	50/40/30	90/70/40	0/10/40	0/10/10
control						90	10

[a] The first, second, and/or third value 00/00/00 denotes IGR inhibition at 10, 5, and 3 μg/nymph, respectively.

The oxime ethers were visualized on TLC plates (as pink spots) by spraying with 2,4-dinitrophenylhydrazine solution. Unlike aromatic carbonyl compounds, which gave instant pink color, the pink spots of oxime ethers on TLC plates emerged fully 15−20 min after the spray. The test compounds were characterized by ^{1}H NMR spectroscopy, elemental analysis, and, whenever necessary, IR and MS spectroscopy. The generic formulas of the sets of compounds (**I**−**XXI**) studied are shown in Figure 1.

A diagnostic one-proton singlet at δ 7.9−8.0 (C**H**=N) was conspicuous in the ^{1}H NMR spectra of all the oxime ethers. The IR spectra of the compounds (**I**−**XXI**) showed characteristic absorption bands around 800 (aromatic), 1500 (−CH=N, str), 1575 (C−C str, aromatic), and 1600 cm^{-1} (N−O−R), which were characteristic of these compounds. The mass spectrum of a representative compound 3-methoxy-4-ethoxybenzaldoxime N−O−ethyl ether (**II**) showed a molecular ion peak at *m*/*z* 223 along with a fragment ion peak at *m*/*z* 195 (M - CH_2=CH_2) due to cleavage with hydrogen migration. The peaks at *m*/*z* 178 and 150 were tentatively attributed to loss of the −OCH_2CH_3 moiety from the *m*/*z* 223 and 195 fragments, respectively. The other fragment ion peaks at *m*/*z* 134 and 124 may arise due to the loss of CH_4 and CN moieties. In all of the oxime ethers, the molecular ion peak was also the base ion peak.

IGR Activity of the Test Chemicals. The oxime ethers (**I**−**XXI**) were screened for their IGR activity against fifth-instar nymphs of *S. gregaria*. The test compounds were either injected into the hemolymph of 2−3-day-old fifth-instar nymphs at 10, 5, and 3 μg/insect or applied topically at 20 and 5 μg/insect. The IGR activity was computed on the basis of total abnormal counts recorded due to nymph−adult intermediates and abnormal adults during and after the last molt. Nymph−adult intermediates included either nymphs with incomplete ecdysis during the last molt or adults with exuviae attached on the ventral side. Abnormal adults, on the other hand, had highly deformed wings, crippled legs, or slight to medium abnormal wings.

Injection into the Hemolymph. When 3-methoxy-4-ethoxybenzaldoxime homologues (**I**−**VII**) were injected into the insect hemolymph at the dose level of 10 μg/nymph, N−O−ethyl (**II**) and N−O−butyl derivative (**V**) exihibited 60% abnormal molts (Table 1). Among 3,4-dimethoxybenzaldoxime derivatives, **IX**−**XI** also gave the same, 60%, abnormalities. Similarly, 3,4-methylenedioxybenzaldoxime homologues such as **XV**, **XVI**, and **XVIII** gave 100, 80, and 80% abnormalities. Nymphal mortality (up to 30%) was recorded for the compounds of the first subseries (**I**−**VII**) as compared to 10% in the standard buprofezin (Applaud) at the injection dose of 10 μg/nymph. Except for **I**, **III**, and **IV**, none of the test chemicals showed any mortality among the newly emerged normal adults.

Of 21 compounds tested by injection at 10 μg, 10 compounds were selected for further bioassay at the lower dose of 5 μg/nymph. The data revealed that with the decrease in injection dose, IGR activity also decreased. The six most active compounds identified in this screen included 3-methoxy-4-ethoxybenzaldoxime N−O−butyl ether (**V**), 3,4-dimethoxybenzaldoxime N−O−*n*-propyl ether (**X**), 3,4-dimethoxybenzaldoxime N−O−isopropyl ether (**XI**), 3,4-methylenedioxybenzaldoxime N−O−methyl ether (**XV**), 3,4-methylenedioxybenzaldoxime N−O−ethyl ether (**XVI**), and 3,4-methylenedioxybenzaldoxime N−O−isopropyl ether (**XVIII**), which inflicted 50, 60, 50, 70, 50, and 70% abnormalities, respectively, during ecdysis. At a still lower dose of 3 μg, compound **XVIII** showed 50% inhibition. The adult emergence at 5- and 3-μg dose levels ranged from 10 to 60% and from 30 to 60%, respectively. Nymphal mortality up to 20% was recorded for almost all test chemicals. The IGR activity of the most active test compounds (**XV** and **XVIII**) was comparable to that of buprofezin (Applaud), a commercial IGR which at the lowest dose level of 3 μg/nymph recorded 40% adult emergence and inflicted 50% total abnormality and 10% nymphal and adult mortality.

Topical Application. Among the three subseries, N−O−alkyl derivatives of 3-methoxy-4-ethoxy benzaldoxime (**I**−**VI**) were more active than those derived from

Table 2. IGR Activity of Oxime Ethers on Fifth-Instar Nymphs of *S. gregaria* F. When Applied Topically at 20 and 5 μg/Nymph (n = 10, R = 2)

test chemical	nymphs dead (%)	nymph−adult intermediates (%)	abnormal adults (%)	total abnormality (%)	normal adults survived (%)	normal adults dead (%)
I		10 (10)[a]	90 (30)	100 (40)	− (60)	
II		50 (10)	40 (20)	90 (30)	10 (70)	
III		30 (0)	50 (20)	80 (20)	20 (80)	
IV		20 (0)	40 (20)	60 (20)	40 (80)	
V		30 (0)	50 (10)	80 (10)	20 (90)	
VI		30 (0)	30 (10)	60 (10)	20 (90)	
VIII		10	10	20	40	40
IX		10	10	20	40	40
X		10	40	50	50	
XI			60	60	30	10
XII		10	40	50	50	
XIII	20		50	50	30	
XV			10	10	90	
XVI		10	40	50	50	
XVII		10	40	50	50	
XVIII			60	60	40	
XIX			40	40	60	
XX			30	30	70	
control					90	10

[a] Values in parentheses denote percent change at 5 μg/nymph.

3,4-dimethoxybenzaldoxime and 3,4-methylenedioxybenzaldoxime (Table 2). At a higher dose level of 20 μg, the N−O−alkyl ethers of 3-methoxy-4-ethoxy benzaldoxime exhibited 60−100% inhibition. The most active compounds were N−O−methyl (**I**), N−O−ethyl (**II**), N−O−*n*-propyl (**III**), and N−O−*n*-butyl (**V**) homologues, which showed >80% inhibition at 20-μg dose level. At the lower dose level, the IGR activity was drastically reduced and the most active compound (**I**) could bring about only 40% inhibition of insect growth. The compounds belonging to the remaining two series were moderately active at 20 μg, the most active being 3,4-dimethoxybenzaldoxime N−O−isopropyl ether (**XI**), which produced 60% total abnormality. To examine the effect of a cyano group, three cyanoethyl derivatives were prepared. The insect growth disruption activity of these compounds was disappointing.

Lipophilicity and Structure−Activity Relationships. The relationship between lipophilicity (R_M value), alkyl chain length, and percent insect growth inhibition is illustrated in Figure 2. Comparison of the data on R_M value and IGR activity (percent abnormality expressed in log value) of the test compounds when administered by injection into insect hemolymph revealed no correlation, however, when applied topically; activity was weakly correlated to lipophilicity. In the case of 3-methoxy-4-ethoxybenzaldoxime N−O−alkyl ethers (**I**−**VI**), the lipophilicity increased linearly with an increase in the number of carbon atoms in the side chain, but there is a gradual fall in their IGR activity at dose level of 5 μg (Figure 2). In the case of 3,4-dimethoxybenzaldoxime N−O−alkyl ethers and 3,4-methylenedioxybenzaldoxime N−O−alkyl ethers, IGR activity first increased with increasing chain length up to three carbon atoms, beyond which it started diminishing. Both series exhibited an optimum R_M value corresponding to the most potent compound. The weak correlation with derivatives of 3,4-dimethoxybenzaldoxime N−O−alkyl ethers and 3,4-methylenedioxybenzaldoxime N−O−alkyl ethers was noted, with isopropyl substitution having consistently highest activity. The fact that the isopropyl substituent confers greatest activity, despite its irregularity with respect to R_M, suggests that steric parameters are also important for imparting activity.

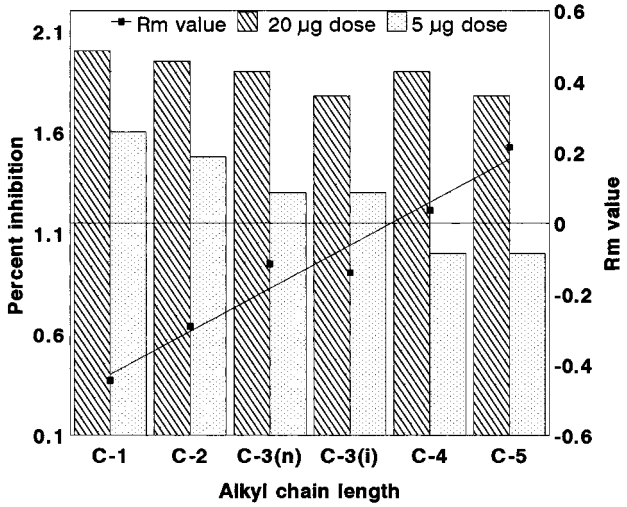


Figure 2. Relationship between R_M value, IGR activity, and alkyl chain length of 3-methoxy-4-ethoxybenzaldoxime N−O−alkyl ethers. [Percent inhibition is expressed as log value (the data refer to topical application).]

In earlier structure−activity relationship studies on a variety of JH active compounds having functions such as ethers, oxime ethers, esters, hydroxylamines, and amines (Nakayama et al., 1985; Niwa et al., 1988; Hayashi et al., 1990, 1991), the common structural features responsible for conferring high JH activity had been suggested to be the overall molecular dimension and a position-specific functional effect. Since the oxime ether group of compounds reported herein has some resemblance to those oxime juvenoides reported earlier, such molecules are expected to behave in a similar mode of action (Hayashi et al., 1991b). It is hoped that a variety of potentially useful juvenoides based on such oxime ethers can be developed for pest control. Because of their diminished lethal action and environmentally benign nature, such compounds have gained of late considerable importance.

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