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Synthesis and Lateral Root–Inducing Activity of Novel 2–Piperidones with a 1,4–Benzodioxan Ring

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A series of novel *N*–benzyl–2–piperidones having a 1,4–benzodioxan ring was synthesized and investigated for their activity to induce lateral roots in the lettuce seedlings. *N*–Benzyl–3–[1–(3,6–benzodioxanyl)–1–hydroxymethyl]–2–piperidone (**23**) induced 100% emergence of lateral roots at 100 ppm. There was no significant difference in activity between the *erythro*– and *threo*–**23**. The introduction of a benzyloxymethyl substituent at the 2–position on the 1,4–benzodioxan ring slightly increased the activity compared with that of **23**, showing some activity even at 1 ppm, while the activity was found to fall off sharply with a methoxy group adjacent to the 1,4–dioxane ring.

INTRODUCTION

We have previously reported that a variety of *N*–benzyl–3–substituted–2–piperidones caused lateral root formation on lettuce seedlings (Tsukada *et al.*, 1999). The results from structure–activity relationship studies indicated that the substituent at the 3–position of 2–piperidone ring significantly affected the activity. Of these compounds tested, *N*–benzyl–3–[1–hydroxy–1–(4–quinolyl)methyl]–2–piperidone (**1**, Fig. 1) was the most effective for inducing lateral roots.

It is known that several natural products with a 1,4–benzodioxan ring such as haedoxan A (Taniguchi *et al.*, 1989), cleomiscosin A (Ray *et al.*, 1980), americanin (Woo *et al.*, 1978) and silybin (Hansel *et al.*, 1972) show some biological activity. It appears

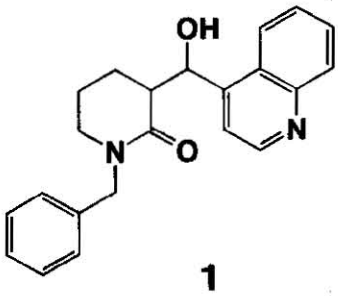


Fig. 1. Structure of *N*–benzyl–3–[1–hydroxy–1–(4–quinolyl) methyl]–2–piperidone (**1**)

that in these compounds the 1,4–benzodioxan moiety is essential for the activity. However, 1,4–benzodioxan derivatives have received little attention as molecules of potential agrochemical interest, and there has been no report in the literature of compounds with a 1,4–benzodioxan ring showing plant growth regulatory activity. We therefore synthesized a series of novel *N*–benzyl–2–piperidones possessing a 1,4–benzodioxan ring at the 3–position and investigated their effects on the growth of lettuce seedlings. This paper describes their synthesis, lateral root–inducing activity and structure–activity relationships.

MATERIALS AND METHODS

Synthesis

All melting points (mp) are uncorrected. ^{1}H–NMR spectra were recorded on JNM–GX400 spectrometer with tetramethylsilane as an internal standard and all samples were prepared in deuterochloroform. Gravity column chromatography was carried out with Merck kiesegel 60 F254 (0.063–0.200 mm, 70–230 mesh ASTM) and Wakogel C–300 (45–75 μm). TLC was performed on precoated 60 F254 silica gel plates (0.25 mm, 0.5 mm, or 1 mm thickness, 20×20 cm) supplied by E. Merck.

4–Benzyloxy–3–hydroxybenzaldehyde **(2).**

To a solution of 3, 4 dihydroxybenzaldehyde (75 g, 0.54 mol) in DMSO (150 ml) was added sodium hydride (60% in oil, washed with hexane, 22 g, 0.54 mol) at 0 °C. After stirring for 1 hr at room temperature, to the mixture was added benzyl chloride (62 ml, 0.54 mol). After stirring for 18 hr at room temperature, the mixture was acidified with conc. HCl solution. The precipitate was collected by filtration and recrystallized from toluene to give pure **2**. Yield 30%. White amorphous solid, mp 78–80 °C. ^{1}H–NMR δ: 1.65 (1H, br, –OH), 5.21 (2H, s, –O–C$\underline{H}_2$–Ph), 7.04 (1H, d, J=8 Hz, Ar–H), 7.38–7.47 (7H, m, Ar–H), 9.84 (1H, s, –CHO).

3–Benzoylmethoxy–4–benzyloxybenzaldehyde **(3)**

To a solution of **2** (10 g, 44 mmol), potassium bicarbonate (12.2 g, 88 mmol), and a catalytic amount of 18–crown–6 in CH_3CN (200 ml) was added phenacyl bromide (10.5 g, 52.8 mmol). After stirring for 24 hr at room temperature, the mixture was filtered through a celite pad. The filtrate was concentrated and to the residue was added ether (500 ml) and water (100 ml). The organic layer was separated, washed with 10% of NaOH solution, water, brine, and dried (Na_2SO_4). Concentration of the solvent followed by recrystallization from ether gave pure **3**. Yield 93%. White amorphous solid, mp 107 °C. ^{1}H–NMR δ: 5.31 (2H, d, J=4 Hz, –O–CH_2–), 5.46 (2H, s, –O–CH_2–), 7.07–7.10 (1H, m, Ar–H), 7.30–7.31 (1H, m, Ar–H), 8.02–8.04 (1H, m, Ar–H), 9.85 (1H, s, –CHO).

4–Benzyloxy–3–(2–hydroxy–2–phenylethoxy)benzaldehyde **(4)**

A solution of **3** (5 g, 14.4 mmol), ammoniun chloride (1.6 g, 30 mmol), trimethyl orthoformate in THF : MeOH=3:1 (150 ml) was heated under refluxing for 8 hr. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution and concentrated. The residue was diluted with EtOAc (500 ml). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, brine, and dried (Na_2SO_4). After removal of the solvent, the residue (crude acetal) was dissolved in THF : MeOH=4:1 (100 ml) and to this solution was added sodium borohydride (272 mg, 7.2 mmol) at 0 °C. After stirring for 1 hr

at 0°C, the mixture was acidified with 2N HCl solution. After stirring for 2 hr, the reaction mixture was concentrated and the residue was diluted with EtOAc (300 ml). The organic layer was separated, washed with 10% of NaOH solution, water, brine, and dried (Na_2SO_4). Concentration followed by column chromatography (silica gel, 50% EtOAc in hexane) gave pure **4**. Yield 90%. Colorless oil. ^{1}H-NMR δ: 3.39 (1H, br, -OH), 4.04–4.13 (1H, m, -O-CH_2-), 4.19–4.23 (1H, m, -O-CH_2-), 5.10 (1H, dd, J=3, 9 Hz, -C<u>H</u>(OH)-), 5.18 (2H, s, -O-CH_2-), 7.02 (1H, d, J=8 Hz, Ar-H), 7.25–7.53 (7H, m, Ar-H), 9.79 (1H, s, -CHO).

4-Hydroxy-3-(2-hydroxy-2-phenylethoxy)benzaldehyde **(5)**

A solution of **4** (6.1 g, 17.5 mmol) and palladium on carbon (5% on carbon, 0.6 g) in EtOAc : MeOH=1:1 (50 ml) was stirred under hydrogen gas. After stirring for 24 hr, the mixture was filtered through a celite pad and the filtrate was concentrated. Recrystallization from diisopropyl ether gave pure alcohol **5** (1.85 g, 41%). White amorphous solid, mp 114°C. ^{1}H-NMR δ: 1.84 (1H, br, -OH), 4.07–4.12 (3H, m, -O-CH_2-, -OH), 4.19–4.22 (1H, m, -O-CH_2-), 5.13 (1H, dd, J=3, 9 Hz, -C<u>H</u>(OH)-), 7.01 (1H, d, J=8 Hz, Ar-H), 7.34–7.42 (6H, m, Ar-H), 9.73 (1H, s, -CHO).

2-Phenyl-1,4-benzodioxan-6-carbaldehyde **(6)**

A solution of **5** (100 mg, 0.38 mmol) and a catalytic amount of *p*-toluenesulfonic acid in toluene (30 ml) was heated under refluxing for 16 hr. After cooling, to the mixture was added Et_3N (50 ml). Concentration followed by column chromatography (silica gel, 25% EtOAc in hexane) gave pure **6**. Yield 58%. White amorphous solid, mp 75–77°C. ^{1}H-NMR δ: 4.06 (1H, dd, J=9 Hz, 12 Hz, -O-CH_2-), 4.43 (1H, dd, J=9, 12 Hz, -O-CH_2-), 5.20 (1H, dd, J=2, 9 Hz, -O-CH-), 7.10 (1H, d, J=8.3 Hz, Ar-H), 7.34–7.52 (7H, m, Ar-H), 9.86 (1H, s, -CHO).

4-Benzyloxy-3-(2,3-epoxypropyloxy)benzaldehyde **(7)**

To a suspension of sodium hydride (60% in oil, washed with hexane, 17.2 g, 0.43 mol) in DMF (250 ml) was added **2** (75 g, 0.33 mmol) at 0°C. After stirring for 1 hr at room temperature, to the mixture was added 1-bromo-2,3-epoxypropane (34 ml, 0.40 mol). After stirring for 18 hr at room temperature, the mixture was quenched with water (200 ml), and diluted with ether (1000 ml) The organic layer was separated, washed with water, 5% NaOH solution, brine and dried (Na_2SO_4). After concentration of the solvent, the residue was recrystallized from EtOH to give pure **7**. Yield 44%. Colorless crystal, mp 94–96°C. ^{1}H-NMR δ: 2.79–2.80 (1H, q, J=2 Hz, -CH(O)C<u>H</u>$_2$), 2.91 (1H, t, J=4 Hz, -CH(O)C<u>H</u>$_2$), 3.40–3.44 (1H, m, -C<u>H</u>(O)CH_2), 4.05–4.09 (1H, dd, J=5, 9 Hz, -O-CH_2-), 4.34–4.40 (1H, dd, J=3, 11 Hz, -O-CH_2-), 5.27 (1H, s, -O-CH_2-), 7.00 (1H, d, J=8.3 Hz, Ar=H), 7.32–7.46 (m, 7H, Ar-H), 9.83 (1H, s, -CHO).

3-(2,3-Epoxypropyloxy)-4-hydroxybenzaldehyde **(8)**

A mixture of **7** (42.5 g, 0.14 mol) and palladium on carbon (5% on carbon, 4.2 g) in EtOAc (250 ml) was stirred under hydrogen gas. After stirring for 2 hr, the mixture was filtered through a celite pad and the filtrate was concentrated. Separation by column chromatography (silica gel, 50% EtOAc in hexane) gave pure **8**. Yield 90%. White amorphous solid, mp 71–72°C. ^{1}H-NMR δ: 2.83–2.84 (1H, m, -CH(O)C<u>H</u>$_2$), 2.97–2.99 (1H, m, -CH(O)C<u>H</u>$_2$), 3.40–3.44 (1H, m, -C<u>H</u>(O)CH_2), 4.04 (1H, dd, J=6, 11 Hz, -O-CH_2-), 4.44 (1H, dd, J=2, 11 Hz, -O-CH_2-), 6.64 (1H, s, -OH), 7.07 (1H, d, J=8.3 Hz, Ar-H), 7.43–7.48 (2H, m, Ar-H), 9.82 (1H, s, -CHO).

2-Hydroxymethyl-1,4-benzodioxan-6-carbaldehyde **(9)**

A mixture of **8** (38 g, 0.14 mol), potassium bicarbonate (55.3 g, 0.4 mol), and 18-crown-6 (3.8 g) in CH_3CN (250 ml) was stirred for 16 hr at room temperature. The mixture was filtered through a celite pad. Concentration of the filtrate followed by column chromatography (silica gel, 50% EtOAc in hexane) gave pure **9**. Yield 43%. White amorphous solid, mp 59–60 °C. ^{1}H-NMR δ: 1.95 (1H, t, J=6 Hz, -OH), 3.86–4.06 (2H, m, -O-CH_2-), 4.14–4.19 (1H, m, -O-CH_2-C<u>H</u>-O-), 4.34–4.39 (2H, m, -C<u>H</u>$_2$-OH), 7.02 (1H, d, J=9 Hz, Ar-H), 7.42–7.44 (2H, m, Ar-H), 9.83 (1H, s, -CHO).

2-Methoxymethyl-1,4-benzodioxan-6-carbaldehyde **(10)**

A mixture of **9** (2 g, 10.3 mmol), sodium hydroxide (4.1 g, 103 mmol), methyl iodide (103 mmol) and tetrabutylammonium hydrogen sulfate (1.77 g, 5.2 mmol) in water-dichloromethane=1:1 (100 ml) was stirred for 72 hr at room temperature. The aqueous layer was separated and the product was extracted with EtOAc (400 ml). The combined organic layer was washed with water, brine and dried (Na_2SO_4). Concentration followed by column chromatography (silica gel, 25% EtOAc in hexane) gave pure **10**. Yield 84%. Colorless oil. ^{1}H-NMR δ: 3.44 (3H, s, -OCH_3), 3.61–3.71 (2H, m, -O-CH_2-), 4.08–4.13 (1H, m, -O-CH_2-C<u>H</u>-O-), 4.30–4.42 (2H, m, -O-CH_2-), 6.90–7.03 (1H, m, Ar-H), 7.40–7.42 (2H, m, Ar-H), 9.82 (1H, s, -CHO).

Compounds **11** and **12** were prepared in the same manner as **10** by using the corresponding alkyl bromide instead of the methyl iodide.

2-Ethoxymethyl-1,4-benzodioxan-6-carbaldehyde **(11)**. Yield 82%. Colorless oil. ^{1}H-NMR δ: 1.14–1.20 (3H, m, -CH_3), 3.48–3.68 (3H, m, -O-CH_2-, -CH-O-), 4.27–4.35 (2H, m, -O-CH_2-), 4.08–4.13 (1H, m, -O-CH_2-C<u>H</u>-O-), 6.94 (1H, d, J=9 Hz, Ar-H), 7.33–7.35 (2H, m, Ar-H), 9.75 (1H, s, -CHO).

2-Benzyloxymethyl-1,4-benzodioxan-6-carbaldehyde **(12)**. Yield 95%. Colorless oil. ^{1}H-NMR δ: 3.66 (1H, m, J=6, 10 Hz, -O-CH_2-), 3.73 (1H, dd, J = 5, 10 Hz, -O-CH_2-), 4.11–4.27 (1H, m, -O-CH_2-C<u>H</u>-O-),4.31–4.42 (2H, m, -O-CH_2-), 6.98 (1H, d, J=9 Hz, Ar-H), 7.25–7.40 (7H, m, Ar-H), 9.79 (1H, s, -CHO).

6-Methoxy-1,4-benzodioxan **(14)**

To a mixture of *m*-chloroperbenzoic acid (80% in water, 25 g, 145 mmol), and potassium fluoride (10.5 g, 181 mmol) in CH_2Cl_2 was added 1,4-benzodioxan-6-carbaldehyde (10 g, 72.4 mmol) in CH_2Cl_2 (100 ml) at 0 °C. After stirring for 40 hr at 0 °C to room temperature, the mixture was filtered through a celite pad and the filtrate was concentrated. To the residue was added 50% NaOH solution (100 ml) and the mixture was stirred for 2 hr. To the mixture was added ether (500 ml) and the aqueous layer was separated, acidified with conc. HCl solution. The product was extracted with ether (500 ml). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, brine, and dried (Na_2SO_4). Concentration of the solvent afforded crude phenol (6-hydroxy-1,4-benzodioxan). A mixture of crude phenol, methyl iodide (31 g, 217 mmol) and potassium carbonate (30 g, 217 mmol) in acetone (250 ml) was heated under refluxing for 6 hr. The mixture was filtered through a celite pad and concentrated. The resulting residue was purified by column chromatography (silica gel, 25% EtOAc in hexane) to give pure **14**. Yield 64%. Colorless oil. ^{1}H-NMR δ: 3.73 (3H, s, -O-CH_3), 4.19 (4H, m, -O-C<u>H</u>$_2$-C<u>H</u>$_2$-O-), 6.40–6.45 (2H, m, Ar-H), 6.76–6.79 (1H, m, Ar-H).

6-Methoxy-1,4-benzodioxan-7-carbaldehyde **(15)**

To a solution of **14** (7.5 g, 45.1 mmol) in DMF (50 ml) was added $POCl_3$ (13 ml, 135 mmol) at 0 °C. After stirring for 5 hr at 100 °C, the mixture was poured into ice-cooled water (500 ml). The solution was neutralized with potassium bicarbonate and extracted with ether (2000 ml). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, brine, and dried (Na_2SO_4). After concentration of the solvent, the residue was recrystallized from diisopropyl ether to give pure **15**. Yield 78%. White amorphous solid, mp 116 °C. ^{1}H-NMR δ: 3.84 (3H, s, -O-CH_3), 4.21–4.24 (2H, m, -O-C<u>H</u>$_2$-CH_2-O-), 4.31–4.33 (2H, m, -O-CH_2-C<u>H</u>$_2$-O-), 6.46 (1H, s, Ar-H), 7.36 (1H, m, Ar-H), 10.27 (1H, s, -CHO).

Methyl 5-methoxy-1,4-benzodioxan-7-carboxylate **(17)**

To a solution of methyl gallate (20 g, 0.11 mol) in 10% aqueous sodium tetraborate solution (800 ml) was added aqueous NaOH solution (26 g in water) and dimethyl sulfate (60 ml) during 3 hr. After stirring for 12 hr at room temperature, the mixture was acidified with conc. HCl solution and extracted with ether (2000 ml). The organic layer was separated, washed with water, brine, and dried (Na_2SO_4). Concentration of the solvent gave crude 5-methoxycarbonyl-3-methoxycatechol **(16)**. A mixture of crude **16**, 1,2-dibromoethane (41 g, 0.22 mol), potassium carbonate (76 g, 0.55 mol) in acetone (250 ml) was heated under refluxing for 6 hr. The mixture was filtered through a celite pad and the filtrate was concentrated. The residue was dissolved in ether (1000 ml), and water (200 ml). The organic layer was separated, washed with 10% NaOH solution, water, brine, and dried (Na_2SO_4). After concentration of the solvent, the residue was recrystallized from diisopropyl ether to afford pure **17**. Yield 21%. Colorless amorphous solid, mp 107 °C. ^{1}H-NMR δ: 3.89 (3H, s, -O-CH_3), 3.93 (3H, s, -O-CH_3), 4.27–4.29 (2H, m, -O-C<u>H</u>$_2$-CH_2-O-), 4.37–4.38 (2H, m, -O-CH_2-C<u>H</u>$_2$-O-), 7.20 (1H, d, J=2 Hz, Ar-H), 7.23–7.30 (2H, m, Ar-H).

5-Methoxy-1,4-benzodioxan-7-carbaldehyde **(19)**

To a mixture of lithium aluminum hydride (4.25 g, 112 mmol) was added **17** (5.0 g, 22.3 mmol) in THF (50 ml) at 0 °C. After stirring for 1.5 hr at room temperature, the mixture was quenched with saturated aqueous $MgSO_4$ solution, and then potassium carbonate (50 g) was added. After stirring for 30 minutes at room temperature, the mixture was filtered through a celite pad and the filtrate was concentrated. The residue was dissolved in EtOAc (500 ml) and water (100 ml). The organic layer was separated, washed with brine, and dried (Na_2SO_4). Concentration of the solvent afforded crude alcohol **18**. To a solution of oxalyl chloride in CH_2Cl_2 (50 ml) was added DMSO (2.38 ml, 33.5 mmol) in CH_2Cl_2 (10 ml) at −78 °C. After stirring for 30 minutes at −78 °C, to the mixture was added crude **18** in CH_2Cl_2 (50 ml) at −78 °C. The solution was stirred for 2 hr at −78 °C and then triethylamine (15.6 ml, 112 mmol) was added at −78 °C. The solution was allowed to warm to room temperature, and then diluted with EtOAc (300 ml) and water (100 ml). The organic layer was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by recrystallization from diisopropyl ether gave pure **19**. Yield 66%. Colorless needle, mp 83 °C. ^{1}H-NMR δ: 3.95 (3H, s, -O-CH_3), 4.30–4.32 (2H, m, -O-C<u>H</u>$_2$-CH_2-O-), 4.40–4.42 (2H, m, -O-CH_2-C<u>H</u>$_2$-O-), 7.08 (1H, s, Ar-H), 7.26 (1H, s, Ar-H), 9.79 (1H, s, -CHO).

5-Methoxy-1,4-benzodioxan-6-carbaldehyde **(21)**

A mixture of 3-methoxycatechol (10 g, 71.4 mmol), 1,2-dibromoethane (20.0 g,

0.107 mol), potassium carbonate (49.3 g, 357 mol) in acetone (250 ml) was heated under refluxing for 6 hr. The mixture was filtered through a celite pad and the filtrate was concentrated. The residue was dissolved in ether (1000 ml), and water (200 ml). The organic layer was separated, washed with 10% NaOH solution, water, brine, and dried (Na_2SO_4). Concentration of the solvent gave crude 5-methoxy-1,4-benzodioxan **(20)**. To a solution of crude **20** in DMF (30 ml) was added $POCl_3$ (4.0 ml, 84.8 mmol) at 0 °C. After stirring for 5 hr at 100 °C, the mixture was poured into ice-cooled water (500 ml). The mixture was neutralized with potassium bicarbonate and extracted with ether (500 ml). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from diisopropyl ether to afford pure **21**. Yield 46%. White amorphous solid, mp 134–137 °C. ^{1}H-NMR δ: 3.95 (3H, s, -O-CH_3), 4.38–4.41 (4H, m, -O-C$\underline{H}_2$-CH_2-O-), 6.59 (1H, d, J=9 Hz, Ar-H), 7.43 (1H, d, J=9, Ar-H), 10.21 (1H, s, -CHO).

N-Benzyl-3-[1-hydroxy-1-(3,6-benzodioxanyl)methyl]-2-piperidone **(23)**

To a solution of diisopropylamine (1.1 ml, 7.92 mmol) in THF (100 ml) was added *n*-butyllithium (4.95 ml, 1.6 M solution in hexane) at −78 °C under nitrogen gas. After stirring for 15 minutes, a solution of *N*-benzyl-2-piperidone (1 g, 5.28 mmol) in THF (2 ml) was added dropwise, and then the mixture was stirred at −78 °C for 30 minutes. To the mixture was added a solution of 1,4-benzodioxan-6-carbaldehyde (1.04 g, 6.34 mmol) in THF (2 ml) was added at −78 °C. After stirring at −78 °C for 3 hr, to the mixture was added saturated aqueous NH_4Cl solution (50 ml) and EtOAc (100 ml). The organic layer was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by column chromatography (silica gel, 50% EtOAc in hexane) gave pure **23** which was a diastereomeric mixture of *erythro* and *threo* (1:1). Yield 88%. ^{1}H-NMR δ: 1.23–1.28 (2H, m, β-H, γ-H), 1.56–1.75 (2H, m, β-H, γ-H,), 2.49–2.56 (0.5H, m, α-H), 2.80–2.83 (0.5H, m, α-H), 3.07–3.11 (1H, m, δ-H), 3.20–3.23 (1H, m, δ-H), 4.24 (2H, s, -O-CH_2-), 4.44–4.78 (3H, m, -C$\underline{H}$(O$\underline{H}$)-, -C$\underline{H}_2$-Ph), 5.14 (0.5H, dd, J=4, 6 Hz, -C$\underline{H}$(OH)-), 6.45 (0.5H, s, -O$\underline{H}$), 6.79–6.91 (2H, m, Ar-H), 7.18–7.34 (6H, m, Ar-H).

erythro- **23** white amorphous solid, mp 132 °C. ^{1}H-NMR δ: 1.56–1.74 (4H, m, β-H, γ-H), 2.79–2.82 (1H, m, α-H), 3.07–3.13 (2H, m, δ-H), 4.25 (4H, s, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 4.45 (1H, d, J=15, -C$\underline{H}_2$-Ph), 4.69–4.70 (1H, m, -O$\underline{H}$), 4.76 (1H, d, J=15 Hz, -C$\underline{H}_2$-Ph), 5.15 (1H, dd, J=3, 6 Hz, -C$\underline{H}$(OH)-), 6.81 (s, 2H, Ar-H), 6.90 (1H, s, Ar-H), 7.18–7.36 (5H, m, Ar-H). Anal. Found: C, 71.28; H, 6.59; N, 3.98%. Calcd. for $C_{12}H_{15}NO$: C, 71.37; H, 6.56; N, 3.96%.

threo- **23** white amorphous solid, mp 132–133 °C. ^{1}H-NMR δ: 1.23–1.38 (2H, m, β-H), 1.72–1.79 (2H, m, γ-H), 2.49–2.55 (1H, m, α-H), 3.20–3.23 (2H, m, δ-H), 4.24 (4H, s, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 4.54 (1H, d, J=15 Hz, -C$\underline{H}_2$-Ph), 4.64 (1H, d, J=10 Hz, -C$\underline{H}$(OH)-), 4.69 (1H, d, J=15 Hz, -C$\underline{H}_2$-Ph), 6.45 (1H, s, -O$\underline{H}$), 6.83–6.96 (3H, m, Ar-H), 7.18–7.37 (5H, m, Ar-H). Anal. Found: C, 71.37; H, 6.63; N, 4.04%. Calcd. for $C_{12}H_{15}NO$: C, 71.37; H, 6.56; N, 3.96%.

Compounds **24–30** were prepared in the same manner as **23** by using the corresponding substituted-1,4-benzodioxan-6-carbaldehydes (**6, 10–12, 15, 19, 21**) instead of 1,4-benzodioxan-6-carbaldehyde.

N-Benzyl-3-[1-hydroxy-1-(5-phenyl-3,6-benzodioxanyl)methyl]-2-piperidone **(24)**. Yield 31%. ^{1}H-NMR δ: 1.63–1.90 (4H, m, β-H, γ-H), 2.36–2.38 (0.5H, m, α-H),

2.82–2.84 (0.5H, m, α-H), 3.10–3.24 (2H, m, δ-H), 4.30–4.77 (5H, m, -C$\underline{H}_2$-Ph, -O-CH$_2$-C$\underline{H}$-O-), 5.00–5.20 (2H, m, -C$\underline{H}$(OH)-, -O$\underline{H}$), 6.73–6.99 (2H, m, Ar-H), 7.05–7.43 (5H, m, Ar-H), 7.69–7.70 (1H, m, Ar-H).

N-Benzyl-3-[1-hydroxy-1-(5-methoxymethyl-3,6-benzodioxanyl)methyl]-2-piperidone **(25)**. Yield 37%. ^{1}H-NMR δ: 1.64–1.73 (4H, m, β-H, γ-H), 2.53–2.54 (0.5H, m, α-H), 2.80–2.82 (0.5H, m, α-H), 3.11–3.12 (1H, m, δ-H), 3.21–3.23 (1H, m, δ-H), 3.42 (1.5H, s, OCH$_3$), 3.43 (1.5H, s, -OCH$_3$), 3.61–3.67 (2H, m, -CH$_2$-O-), 4.05–4.15 (1H, m, -O-CH$_2$-C$\underline{H}$-O-), 4.27–4.33 (2H, m, -CH$_2$-O), 4.37–4.78 (1.5H, m, -C$\underline{H}$(OH)-, -C$\underline{H}_2$-Ph), 5.14 (0.5H, s, -C$\underline{H}$(OH)-), 6.46 (1H, s, -O$\underline{H}$), 6.83–7.01 (3H, m, Ar-H), 7.18–7.37 (5H, m, Ar-H).

N-Benzyl-3-[1-(5-ethoxymethyl-3,6-benzodioxanyl)-1-hydroxymethyl]-2-piperidone **(26)**. Yield 36%, ^{1}H-NMR δ: 1.20–1.27 (7H, m, β-H, γ-H, -CH$_2$-C$\underline{H}_3$), 2.37–2.38 (1H, m, α-H), 3.21–3.23 (2H, m, δ-H), 3.54–3.71 (6H, m, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-, -O-C$\underline{H}_2$-CH$_3$), 4.04–4.13 (1H, m, -O-CH$_2$-C$\underline{H}$-O-), 4.28–4.31 (1H, m, -C$\underline{H}$(OH)-), 4.52–4.67 (2H, m, -CH$_2$-Ph), 6.47 (1H, s, -O$\underline{H}$), 6.82–6.93 (3H, m, Ar-H), 7.25–7.37 (5H, m, Ar-H).

N-Benzyl-3-[1-(5-benzyloxymethyl-3,6-benzodioxanyl)-1-hydroxymethyl]-2-piperidone **(27)**. Yield 64%. ^{1}H-NMR δ: 1.63–1.73 (4H, m, β-H, γ-H), 2.52–2.53 (1H, m, α-H), 3.10–3.23 (2H, m, δ-H), 3.66–3.77 (2H, m, -O-CH$_2$-), 4.06–4.15 (1H, m, -O-CH$_2$-C$\underline{H}$-O-), 4.28–4.32 (2H, m, -O-CH$_2$-), 4.45–4.77 (4H, m, -CH$_2$-Ph, -CH$_2$-Ph), 5.15 (1H, s, -C$\underline{H}$(OH)-), 6.46 (1H, s, -O$\underline{H}$), 6.82–6.93 (2H, m, Ar-H), 7.18–7.35 (11H, m, Ar-H).

N-Benzyl-3-[1-hydroxy-1-(2-methoxy-3,6-benzodioxanyl)methyl]-2-piperidone **(28)**. Yield 43%. ^{1}H-NMR δ: 1.38–1.46 (2H, m, β-H), 1.61–1.67 (1H, m, γ-H), 1.75–1.80 (1H, m, γ-H), 2.62–2.69 (1H, m, α-H), 3.21–3.25 (2H, m, δ-H), 3.87 (3H, s, -OCH$_3$), 4.23–4.35 (4H, m, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 4.52 (1H, d, J=15 Hz, -CH$_2$-Ph), 4.73 (1H, d, J=15 Hz, -CH$_2$-Ph), 5.12 (1H, d, J=10 Hz, -CH$_2$-Ph), 6.30 (1H, s, -O$\underline{H}$), 6.54 (1H, d, J=10 Hz, Ar-H), 7.01 (1H, d, J=9 Hz, Ar-H), 7.23–7.37 (5H, m, Ar-H).

N-Benzyl-3-[1-hydroxy-1-(3-methoxy-4,7-benzodioxanyl)methyl]-2-piperidone **(29)**. Yield 44%. ^{1}H-NMR δ: 1.32–1.33 (1H, m, β-H), 1.61–1.80 (3H, m, β-H, γ-H), 2.20 (1H, s, -OH), 2.45–2.54 (1H, m, α-H), 3.18–3.45 (2H, m, δ-H), 3.89 (3H, s, -OCH$_3$), 4.24–4.31 (4H, m, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 4.53–4.75 (3H, m, -C$\underline{H}$(OH)-, -C$\underline{H}_2$-Ph), 6.50–6.63 (2H, m, Ar-H), 7.22–7.37 (5H, m, Ar-H).

N-Benzyl-3-[1-hydroxy-1-(2-methoxy-4,7-benzodioxanyl)methyl]-2-piperidone **(30)**. Yield 70%, ^{1}H-NMR δ: 1.37–1.65 (4H, m, β-H, γ-H), 2.52–2.57 (0.5H, m, α-H), 2.89–2.92 (0.5H, m, α-H), 3.12–3.17 (1H, m, δ-H), 3.20–3.26 (1H, m, δ-H), 3.73 (3H, s, -OCH$_3$), 3.91 (0.5H, d, J=6, -OH), 4.20–4.49 (4H, m, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 4.49–4.57 (1H, m, -CH$_2$-Ph), 4.69–4.79 (1H, m, -CH$_2$-Ph), 5.19 (0.5H, d, J=9 Hz, -C$\underline{H}$(OH)-), 5.69 (0.5H, dd, J=4, 6 Hz, -C$\underline{H}$(OH)-), 6.25 (0.5H, s, Ar-H), 6.39 (1H, d, J=3 Hz, Ar-H), 7.04 (1H, d, J=10 Hz, Ar-H), 7.23–7.34 (5H, m, Ar-H).

Lettuce seedling test

The bioassay using lettuce seedlings (*Lactuca sativa* L.c.v. Sacramento) was performed according to the method described previously (Tsukada *et al.*, 1999). After 7 days of incubation, the length of the primary roots was measured and the emergence of

the visible lateral roots was inspected. The growth rates were calculated as percentages of the averaged lengths of primary roots of treated plants to those of controls (deionized water). A primary root was considered responsive when it contained at least one lateral root. In controls the percentage of emerged lateral roots was less than 2%.

RESULTS AND DISCUSSIONS

Synthesis

Substituted 1,4-benzodioxancarbaldehydes, key intermediates for synthesis of *N*-benzyl-3-[1-hydroxy-1-(substituted 3,6-benzodioxanyl)methyl]-2-piperidones, were prepared according to the route depicted in Fig. 2 and 3. 2-Substituted-1,4-benzodioxan-6-carbaldehydes **6, 10–12** (Fig. 2) and 7-methoxy-1,4-benzodioxan-6-carbaldehyde (**15**, Fig. 3) were synthesized by the procedure previously used for the synthesis of haedoxan A analogs (Taniguchi *et al.*, 1992). Ketone **3** was prepared from 4-benzyloxy-3 hydroxybenzaldehyde (**2**, Kessar *et al.*, 1983) and phenacyl bromide. Conversion

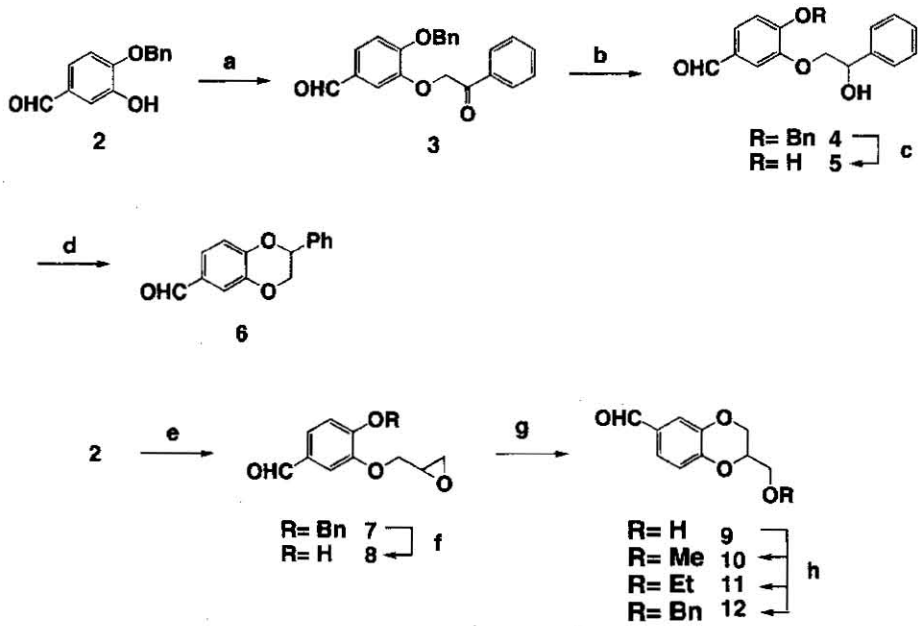


Fig. 2. Synthesis of 2-substituted-1,4-benzodioxan-6-carbaldehydes
Reagents and conditions: (a) phenacyl bromide, K_2CO_3, 18-crown-6, CH_3CN, room temperature; (b) 1) trimethyl orthoformate, NH_4Cl, THF : MeOH=3:1, reflux, 2) $NaBH_4$, THF : MeOH=4:1, 0°C to room temperature, 3) 2N HCl solution, room temperature; (c) Pd/C, EtOAc : MeOH=1:1, room temperature; (d) pyridinium *p*-toluenesulfonate, toluene, reflux; (e) 1-bromo-2,3-epoxypropane, NaH, DMF, 0°C to room temperature; (f) Pd/C, EtOAc, room temperature; (g) K_2CO_3, 18-crown-6, CH_3CN, room temperature; (h) alkyl bromide or iodide, NaOH, tetrabutylammonium hydrogen sulfate, water-CH_2Cl_2=1:1, room temperature.

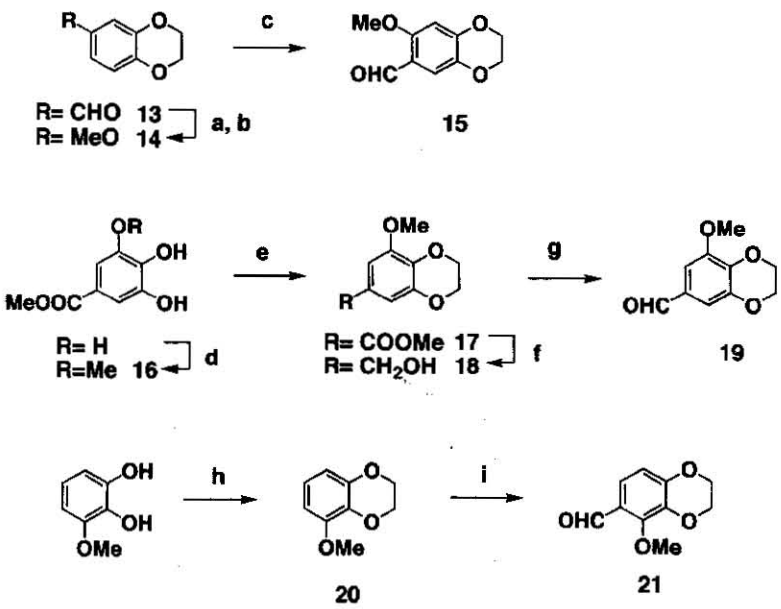
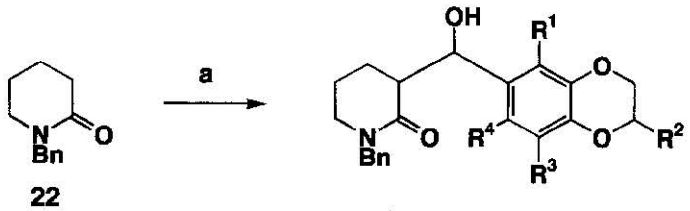


Fig. 3. Synthesis of 1,4-benzodioxan-6-carbaldehydes with a methoxy group
Reagents and conditions: (a) 1) *m*-chloroperbenzoic acid, KF, CH_2Cl_2, 0°C-room temperature, 2) aq. NaOH, room temperature; (b) K_2CO_3, MeI, acetone, reflux; (c) $POCl_3$, DMF, 100°C; (d) NaOH, sodium tetraborate solution, Me_2SO_4, room temperature; (e) K_2CO_3, 1,2-dibromoethane, acetone, reflux; (f) $LiAlH_4$, THF, 0°C to room temperature; (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C; (h) K_2CO_3, 1,2-dibromoethane, acetone, reflux; (i) $POCl_3$, DMF, 100°C.

of **3** into alcohol **4** was executed by the following three-step sequence: (i) acetalization of the formyl group; (ii) reduction of the keto group by sodium borohydride; (iii) deacetalization under acidic conditions. Successive debenzylation of **4** with palladium on carbon afforded phenol **5**, which was cyclized to 2-phenyl-1,4-benzodioxan **6** by treatment with a catalytic amount of *p*-toluenesulfonic acid.

Reaction of **2** with 1-bromo-2,3-epoxypropane gave epoxide **7**. Debenzylation of **7** with palladium on carbon followed by cyclization with potassium carbonate provided 2-hydroxymethyl-1,4-benzodioxan **9**. Alkylation of **9** with the corresponding alkyl bromide or iodide using tetrabutylammonium hydroxide as a base afforded alkyl ethers **10–12**.

1,4-Benzodioxancarbaldehydes having a methoxy group at the different position on the benzene ring were prepared by three procedures as shown in Fig. 3. The Bayer-Villiger oxidation of 1,4-benzodioxan-6-carbaldehyde **(13)** with *m*-chloroperbenzoic acid followed by alkaline hydrolysis afforded 6-hydroxy-1,4-benzodioxan, which was alkylated with methyl iodide and potassium carbonate to yield 6-methoxy-1,4-benzodiox-



R^1	R^2	R^3	R^4	No.
H	H	H	H	23
H	Ph	H	H	24
H	CH_2OMe	H	H	25
H	CH_2OEt	H	H	26
H	CH_2OBn	H	H	27
MeO	H	H	H	28
H	H	MeO	H	29
H	H	H	MeO	30

Fig. 4. Synthesis of *N*-benzyl-3-[1-(3,6-benzodioxanyl)-1-hydroxymethyl]-2-piperidone and related compounds
Reagents and conditions: (a) lithium diisopropylamide, aldehyde, THF, −78 °C.

an **(14)**. Regioselective formylation by the Vilsmeier reaction gave aldehyde **15** in a 78% yield. Treatment of methyl 3,4,5-trihydroxybenzoate with dimethyl sulfate in the presence of sodium tertaborate and sodium hydroxide (Scheline, 1966) afforded 3-methoxy-5-methoxycarbonylcatechol **(16)**, which was cyclized to 1,4-benzodioxan **17** with 1,2-dibromoethane and potassium carbonate. Reduction of **17** with lithium aluminum hydride, followed by Swern oxidation, gave aldehyde **19**. 5-Methoxy-1,4-benzodioxan-6-carbaldehyde **(21)** was prepared from 3-methoxycatechol. Cyclization of 3-methoxycatechol to 5-methoxy-1,4-benzodioxan **(20)** was accomplished in the same manner as that used for compound **17**. Formylation of **20** using the same Vilsmeier reaction employed in the synthesis of **15** afforded the desired aldehyde **21**.

N-Benzyl-2-piperidone **(22)** was prepared according to the procedure reported previously (Tsukada *et al.*, 1999). The lithium enolate of **22** generated with lithium diisopropylamide (LDA) in THF was treated with various 1,4-benzodioxan-6-carbaldehydes to give a mixture of *erythro* and *threo* aldol products **23–30** (Fig. 4). An attempt was made to separate two diastereomeric isomers of **23**. In this aldol reaction, the thermodynamically preferred *erythro*-**23** was obtained as the major product when the reaction mixture was stirred at −78 °C for 3 hours, while under a shorter reaction time (1 hour) *threo*-**23** was formed in preference to the *erythro* isomer. Thus, the *erythro*- and *threo*-**23** were isolated from the reaction mixture under the former and the latter

conditions, respectively, using column chromatography on silica gel. Confirmation of the stereochemistry of the *erythro*– and *threo*–**23** was based on the observation of their ^{1}H–NMR spectra which showed the different coupling constant between 3–H and 1'–H (δ 5.15 ppm, $J_{3\text{-}1'}$=3 Hz for 1'–H of *erythro*; and δ 4.64 ppm, $J_{3\text{-}1'}$=10 Hz for 1'–H of *threo*) (House *et al.*, 1973).

Lateral root–inducing activity

Table 1 shows the effect of a series of *N*–benzyl–2–piperidones with a 1,4–benzodioxan moiety at the 3 position on the growth of lettuce seedlings. Most of the compounds inhibited the growth of primary root less than 50% of the control value at 100 ppm. In seedlings treated with 100 ppm of the 1,4–benzodioxan analog **23**, which is a 1:1 mixture of *erythro* and *threo*, all of the primary roots formed lateral roots, however, its activity rapidly decreased at 10 ppm. Since there was no significant difference in lateral root–inducing activity between the *erythro*– and *threo*–**23**, the activity of other benzodioxan analogs was evaluated for the diastereomeric mixtures.

A modification was first made by introducing a phenyl **(24)**, methoxymethyl **(25)**, ethoxymethyl **(26)** or benzyloxymethyl **(27)** group at the 2–position on the 1,4–bezodioxan ring of compound **23**. Compounds **24–26** had almost the same activity as that of non–substituted benzodioxan analog **23**, while the benzyloxymethyl analog **27** possessed slightly higher activity than **23**, showing 16% emergence of lateral roots even at 1 ppm. These results indicate that a substituent at the 2–position on the 1,4–bezodioxan ring did not significantly involve in lateral root–inducing activity.

The introduction of a methoxy group at the 5– **(28)** or 8– **(29)** position on the 1,4–benzodioxan ring drastically decreased the activity compared with that of **23**, whereas the stimulation of the primary root growth was observed by treatment of these compounds at low concentrations. The 2–methoxy–4,7–benzodioxan analog **30** showed lateral root–inducing activity comparable to that of **23**. It is noteworthy that the activity was greatly affected by a methoxy group adjacent to the 1,4–dioxane ring.

Table 1. Effects of *N*–benzyl–3–[1–hydroxy–1–(substituted–3,6–benzodioxanyl)methyl]–2–piperidones on root growth of lettuce seedlings

	Growth rate of primary root (% of control)			Emergence of lateral root (%)		
No. Conc. (ppm)	100	10	1	100	10	1
23[a]	12	54	106	100	3	0
erythro–**23**	14	44	98	100	30	5
threo–**23**	24	72	103	100	6	0
24	29	50	86	100	21	0
25	30	77	70	100	2	0
26	50	93	100	100	15	0
27	28	77	78	100	16	16
28	40	131	127	37	0	0
29	50	121	101	0	0	0
30	13	54	96	100	11	0

[a] A 1:1 mixture of *erythro* and *threo*

Although compounds **23** and **27** were less active than compound **1**, which is the most effective among the compounds tested so far, this new series of 2–piperidones with a 1,4–benzodioxan ring is worthy of further investigation toward the development of a structurally novel class of plant growth regulators. More detailed studies on the structure–activity relationships are under way.

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