Synthesis and Herbicidal Activity of 1*H*-1,4-Benzodiazepine-2,5-diones

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A series of 1*H*-1,4-benzodiazepine-2,5-diones, which have been found to inhibit photosystem II electron transport, were evaluated for their herbicidal activity. Many of the analogues tested exhibited moderate to good herbicidal activity both preemergence and postemergence. The structure−activity relationships were probed by substitution in both the benzene and diazepine ring. Among the variations investigated, it was found that maximal herbicidal activity was obtained by substitution at C-7 and C-9 in the aromatic portion and by bulky aliphatic substitution at N-4 while leaving N-1, C-6, and C-8 unsubstituted.

Keywords: *1,4-Benzodiazepine-2,5-diones; herbicides; synthesis; photosystem II inhibitors*

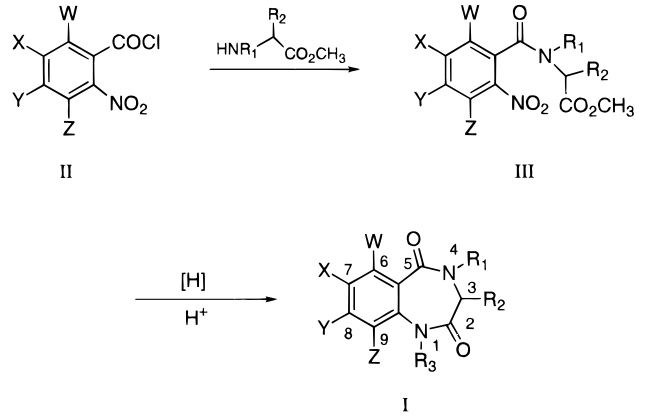
INTRODUCTION

1*H*-1,4-Benzodiazepine-2,5-diones have been widely studied as medicinal agents. Variously, they have been reported to have anxiolytic activity (Wright et al., 1978), anticonvulsant activity (De Martino et al., 1983), and antitumor activity (Jones et al., 1990). More recently they have been studied as potential glycoprotein antagonists (McDowell et al., 1994; Webb et al., 1994). Recently, we disclosed the herbicidal properties of benzodiazepinediones (Guaciaro et al., 1995; Karp et al., 1995). Biochemical studies have shown that the primary mode of action of these compounds is the inhibition of photosynthesis by blocking photosystem II (PS II) electron transport (Singh et al., 1996). The herbicidal activity of these compounds was examined through a systematic screening program of a variety of substituted benzodiazepinediones. In general, the target compounds were prepared in three steps (Scheme 1). Occasionally, further functionalization of the benzodiazepinedione moiety was carried out. A variety of substituent modifications were made to the benzodiazepinedione nucleus, including variation of substituents at all four benzenoid positions (C-6 to C-9) and variation in the diazepine ring (N-1, C-3, and N-4). Herein we report the effect of these substituent modifications on herbicidal activity.

MATERIALS AND METHODS

Chemical Section. *Synthetic Methods.* All reactions requiring anhydrous conditions were carried out under an atmosphere of N_2. Melting points are uncorrected. ^{1}H NMR spectra were obtained on a Varian Unity 300 or XL 300 and measured in $CDCl_3$ or DMSO-d_6. ^{1}H-Coupling constants, J, are reported in hertz. Chemical ionization mass spectra (MS) were recorded on a Finnegan-MAT TSQ4500 spectrometer and are reported in units of m/z. Elemental analyses were performed by Microlit Laboratories, Caldwell, NJ. Flash chromatography was performed on 230−400 mesh silica gel. Analytical thin-layer chromatography was done with glass-backed silica plates, 250 μm (Analtech). Unless otherwise indicated, materials were obtained from commercial suppliers and were used without further purification. 4-Bromo-2-nitrobenzoic acid and 5-fluoro-2-nitrobenzoic acid were prepared as previously described (Erickson et al., 1952). *N*-Alkyl amino esters were prepared from alkylamines and methyl bromoacetate (Karp, 1995). *N*-Arylamino esters were prepared as previously described (Baker et al., 1949).

Scheme 1. Preparation of Benzodiazepinedione Ring System



Benzodiazepinediones **1**−**21** were prepared as shown in Scheme 1. Substituted *o*-nitrobenzoyl chlorides (II), obtained by treatment of the respective *o*-nitrobenzoic acids with thionyl chloride, were reacted with substituted glycines to give the *o*-nitrohippuric esters (III). Reduction of the nitro group was followed by cyclization to afford the title compounds I. Tetrahydropyrrolobenzodiazepinediones **36** and **37** have been described elsewhere (Wright et al., 1978).

Halo- and dihalobenzodiazepinediones **21** and **23**−**25** and vinyl- and alkynyl-substituted benzodiazepinediones **31, 32, 34,** and **35** have been described previously (Karp, 1995).

Preparation of Benzodiazepinediones. *General Procedure. o*-Nitrohippuric esters were reduced catalytically, and the crude *o*-aminohippuric esters were cyclized under acidic conditions as reported previously for compounds **1** and **2** (Karp, 1995). The following compounds were obtained in similar fashion.

7-Chloro-4-isopropyl-1H-1,4-benzodiazepine-2,5-dione (3). Methyl 5-chloro-β-isopropyl-2-nitrohippurate gave compound **3**, which was obtained as a white solid in 75% yield after trituration in EtOAC/hexane: mp 203−205 °C; ^{1}H NMR ($CDCl_3$) δ 10.00 (br s, 1H), 7.72 (d, J = 2.4, 1H), 7.20 (dd, J = 2.4, 8.4, 1H), 6.90 (d, J = 8.4, 1H), 4.84 (septet, J = 6.9, 1H), 3.59 (s, 2H), 1.09 (d, J = 6.9, 6H); MS 253 (MH^+). Anal. Calcd for $C_{12}H_{13}ClN_2O_2$: C, 57.04; H, 5.19; N, 11.09. Found: C, 57.18; H, 5.13; N, 11.08.

7-Chloro-4-(2,2-dimethylpropyl)-1H-1,4-benzodiazepine-2,5-dione (4). Methyl 5-chloro-β-(2,2-dimethylpropyl)-2-nitrohippurate gave compound **4** in 64% as tan needles after recrystallization (EtOH/$H_2$0): mp 195−196 °C; ^{1}H NMR (DMSO-d_6) δ 10.56 (br s, 1H), 7.66 (d, J = 2.7, 1H), 7.51 (dd, J = 2.7, 8.7,

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1H), 7.10 (d, J = 8.7 1H), 3.89 (br s, 2H), 3.39 (br s, 2H), 0.91 (s, 9H); MS 281 (MH^+). Anal. Calcd for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.76; H, 6.32; N, 9.96.

7-Chloro-4-(2,2-dimethylpropyl)-3-methyl-1H-1,4-benzodiazepine-2,5-dione (5). Methyl 5-chloro-β-(2,2-dimethylpropyl)-α-methyl-2-nitrohippurate gave compound **5** as a white foam in 92% yield as a 3/1 mixture of rotational isomers after flash chromatography (EtOAc/CH_2Cl_2, 10/90): mp 153−154 °C; ^{1}H NMR ($CDCl_3$) δ (major) 9.77 (br s, 1H), 7.97 (d, J = 2.5, 1H), 7.39 (dd, J = 2.6, 8.6, 1H), 7.01 (d, J = 8.6, 1H), 4.21 (m, 1H), 3.97 (d, J = 13.6, 1H), 3.08 (d, J = 13.7, 1H), 1.28 (d, J = 7.6, 3H), 1.02 (d, 9H), (minor, partial) 9.60 (br s, 1H), 2.80 (m, 1H), 1.51 (d, J = 7.2, 3H), 0.94 (s, 9H); MS 295 (MH^+).

7-Chloro-4-cyclopentyl-1H-1,4-benzodiazepine-2,5-dione (6). Methyl 5-chloro-β-cyclopentyl-2-nitrohippurate gave compound **6**, which was obtained in 51% yield as white plates after recrystallization (EtOH/H_2O): mp 215.5−217 °C; ^{1}H NMR ($CDCl_3$) δ 9.74 (br s, 1H), 7.91 (d, J = 2.4, 1H), 7.36 (dd, J = 2.4, 8.7, 1H), 6.98 (d, J = 8.7, 1H), 5.07 (quintet, J = 8.4, 1H), 3.76 (s, 2H), 2.00−1.60 (m, 8H); MS 279 (MH^+). Anal. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found: C, 60.00; H, 5.71; N, 9.67.

7-Chloro-4-cyclobutyl-1H-1,4-benzodiazepine-2,5-dione (7). Methyl 5-chloro-β-cyclobutyl-2-nitrohippurate gave compound **7**, which was obtained in 57% yield as white plates after recrystallization (EtOH/H_2O): mp 205−206 °C; ^{1}H NMR ($CDCl_3$) δ 9.76 (br s, 1H), 7.89 (d, J = 2.4, 1H), 7.38 (dd, J = 2.4, 8.4, 1H), 6.99 (d, J = 8.4, 1H), 5.14 (quintet, J = 8.7, 1H), 3.92 (s, 2H), 2.27−2.19 (m, 4H) 1.80−1.70 (m, 2H); MS 265 (MH^+). Anal. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 59.22; H, 4.90; N, 10.45.

7-Chloro-4-cyclopropyl-1H-1,4-benzodiazepine-2,5-dione (8). Methyl 5-chloro-β-cyclopropyl-2-nitrohippurate gave compound **8** in 62% yield as white crystals after recrystallization (CH_2Cl_2): mp 185−186 °C; ^{1}H NMR (DMSO-d_6) δ 10.50 (br s, 1H), 7.70 (d, J = 2.7, 1H), 7.53 (dd, J = 2.6, 8.6, 1H), 7.08 (d, J = 8.4, 1H), 3.80 (s, 2H), 2.96 (m, 1H), 0.73 (m, 4H); MS 251 (MH^+). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.47; H, 4.21; N, 11.22.

4-Allyl-7-chloro-1H-1,4-benzodiazepine-2,5-dione (9). Methyl 5-chloro-β-allyl-2-nitrohippurate gave compound **9** in 75% yield as white crystals after recrystallization (CH_2Cl_2): mp 191−192 °C; ^{1}H NMR (DMSO-d_6) δ 10.50 (br s, 1H), 7.70 (d, J = 2.4, 1H), 7.55 (dd, J = 2.7, 8.7, 1H), 7.11 (d, J = 8.4, 1H), 5.77 (m, 1H), 5.19 (m, 2H), 4.15 (d, J = 5.4, 2H), 3.83 (s, 2H); MS 251 (MH^+). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.34; H, 4.53; N, 11.04.

7-Chloro-4-propargyl-1H-1,4-benzodiazepine-2,5-dione (10). Methyl 5-chloro-β-propargyl-2-nitrohippurate gave compound **10**, which was obtained in 25% yield as a white solid after flash chromatography (EtOAc/CH_2Cl_2, 25−50%): mp 207−209 °C; ^{1}H NMR (DMSO-d_6) δ 10.50 (br s, 1H), 7.70 (d, J = 2.4, 1H), 7.56 (dd, J = 2.6, 8.6, 1H), 7.11 (d, J = 8.4, 1H), 4.37 (d, J = 2.7, 2H), 3.96 (s, 2H), 3.27 (t, J = 2.4, 1H); MS 249 (MH^+). Anal. Calcd for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.65; N, 11.27. Found: C, 57.68; H, 3.65; N, 11.20.

7-Chloro-4-furfuryl-1H-1,4-benzodiazepine-2,5-dione (11). Methyl 5-chloro-β-furfuryl-2-nitrohippurate gave compound **11** in 38% yield as yellow crystals after recrystallization (CH_2Cl_2): mp 179−180 °C; ^{1}H NMR (DMSO-d_6) δ 10.50 (br s, 1H), 7.71 (d, J = 2.4, 1H), 7.57 (s, 1H), 7.55 (dd, J = 2.5, 8.5, 1H), 7.10 (d, J = 8.7, 1H), 6.39 (d, J = 1.2, 2H), 4.74 (s, 2H), 3.89 (s, 2H); MS 291 (MH^+). Anal. Calcd for $C_{14}H_{11}ClN_2O_3$: C, 57.84; H, 3.81; N, 9.64. Found: C, 57.64; H, 3.74; N, 9.49.

7-Chloro-4-(3,5-difluorophenyl)-1H-1,4-benzodiazepine-2,5-dione (12). Methyl 5-chloro-β-(3,5-difluorophenyl)-2-nitrohippurate gave compound **12** in 71% yield as tan crystals after recrystallization (CH_2Cl_2/heptane): mp 218−219 °C; ^{1}H NMR (DMSO-d_6) δ 10.80 (br s, 1H), 7.77 (d, J = 2.4, 1H), 7.62 (dd, J = 2.7, 8.8, 1H), 7.22 (m, 4H), 4.29 (s, 2H); MS 323 (MH^+). Anal. Calcd for $C_{15}H_9ClF_2N_2O_2$: C, 55.83; H, 2.81; N, 8.68. Found: C, 55.78; H, 2.76; N, 8.72.

7-Chloro-4-(3-(trifluoromethyl)phenyl)-1H-1,4-benzodiazepine-2,5-dione (13). Methyl 5-chloro-β-(3-(trifluoromethyl)phenyl)-2-nitrohippurate gave compound **13**, which was obtained in 79% yield as an off-white solid after chromatography (EtOAc/CH_2Cl_2, 5−10%): mp 217−218 °C; ^{1}H NMR (DMSO-d_6) δ 10.80 (br s, 1H), 7.73 (m, 6H), 7.20 (d, J = 8.7, 1H), 4.30 (s, 2H); MS 355 (MH^+). Anal. Calcd for $C_{16}H_{10}ClF_3N_2O_2$: C, 54.18; H, 2.84; N, 7.90. Found: C, 53.89; H, 2.92; N, 7.70.

7-Chloro-4-(4-methoxyphenyl)-1H-1,4-benzodiazepine-2,5-dione (14). Methyl 5-chloro-β-(4-methoxyphenyl)-2-nitrohippurate gave compound **14** in 72% yield as beige plates after recrystallization (EtOH/H_2O): mp 222−224 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 10.15 (br s, 1H), 7.80 (d, J = 1.8, 1H), 7.26 (dd, J = 2.4, 8.7, 1H), 7.19 (d, J = 9.0, 2H), 6.95 (d, J = 9.0, 1H), 6.79 (d, J = 8.7, 2H), 4.07 (s, 2H), 3.67 (s, 3H); MS 317 (MH^+). Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 60.54; H, 3.98; N, 8.78.

4-tert-Butyl-9-methyl-1H-1,4-benzodiazepine-2,5-dione (15). Methyl 3-methyl-β-*tert*-butyl-2-nitrohippurate gave compound **15**, which was obtained in 74% yield as an off-white solid after chromatography (EtOAc/hexanes, 30/70): mp 169−171.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.80 (br s, 1H), 7.69 (d, J = 7.8, 1H), 7.24 (d, J = 7.5, 1H), 7.08 (t, J = 7.5, 1H), 4.00−3.70 (m, 2H), 2.31 (s, 3H), 1.53 (s, 9H); MS 247 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.20; H, 7.47; N, 11.29.

4-tert-Butyl-7-methyl-1H-1,4-benzodiazepine-2,5-dione (16). Methyl 5-methyl-β-*tert*-butyl-2-nitrohippurate gave compound **16**, which was obtained in 72% yield as a white solid after chromatography (EtOAc/hexanes, 30/70): mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 9.45 (br s, 1H), 7.74 (br s, 1H), 7.19 (dd, J = 2.1, 8.4, 1H), 6.88 (d, J = 8.4, 1H), 3.87 (br s, 2H), 2.32 (s, 3H), 1.55 (s, 9H); MS 247 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.17; H, 7.38; N, 11.25.

4-tert-Butyl-6-methyl-1H-1,4-benzodiazepine-2,5-dione (17). Methyl 6-methyl-β-*tert*-butyl-2-nitrohippurate gave compound **17**, which was obtained in 31% yield as a white solid after chromatography (EtOAc/hexanes, 25−30%): mp 198−201 °C; ^{1}H NMR ($CDCl_3$) δ 9.33 (br s, 1H), 7.15 (t, J = 7.8, 1H), 6.98 (d, J = 7.8, 1H), 6.77 (d, J = 7.8, 1H), 3.96 (d, J = 14.7, 1H), 3.80 (d, J = 14.7, 1H), 2.44 (s, 3H), 1.55 (s, 9H); MS 247 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.10; H, 7.40; N, 11.31.

4-tert-Butyl-7-methoxy-1H-1,4-benzodiazepine-2,5-dione (18). Methyl 5-methoxy-β-*tert*-butyl-2-nitrohippurate gave compound **18** in 76% yield as a tan solid: mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 9.53 (br s, 1H), 7.41 (d, J = 2.4, 1H), 6.97−6.88 (m, 2H), 4.00−3.75 (br s, 2H), 3.80 (s, 3H), 1.55 (s, 9H); MS 263 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 63.98; H, 6.86; N, 10.44.

4-tert-Butyl-7,9-dimethyl-1H-1,4-benzodiazepine-2,5-dione (19). Methyl 3,5-dimethyl-β-*tert*-butyl-2-nitrohippurate gave compound **19** in 74% yield as a yellow solid after chromatography (CH_2Cl_2, followed by EtOAc/CH_2Cl_2, 5−15%): mp 186−187 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 7.55 (d, J = 1.2, 1H), 7.10 (d, J = 1.2, 1H), 4.10−3.60 (br d, 2H), 2.31 (s, 6H), 1.57 (s, 9H); MS 261 (MH^+). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.12; H, 7.77; N, 10.66.

4-tert-Butyl-7-fluoro-1H-1,4-benzodiazepine-2,5-dione (20). Methyl 5-fluoro-β-*tert*-butyl-2-nitrohippurate gave compound **20**, which was isolated in 26% yield as an orange solid after chromatography (EtOAc/heptane, 50/50): mp 119−120 °C; ^{1}H NMR ($CDCl_3$) δ 9.70 (br s, 1H), 7.52 (dd, J = 4.7, 9.1, 1H), 7.46 (dd, J = 2.9, 8.8, 1H), 7.14 (m, 1H), 4.20−4.10 (br s, 1H), 3.70−3.50 (br s, 1H), 1.50 (s, 9H); MS 251 (MH^+).

4-tert-Butyl-7-chloro-9-methyl-1H-1,4-benzodiazepine-2,5-dione (22). A solution of compound **15** (1.00 g, 4.10 mmol) in acetic acid (10 mL) containing a few grains of ferric chloride hexahydrate was treated with an excess of chlorine, and the solution was allowed to stir at room temperature for 3 d. After this time, the solution was poured into water and extracted with EtOAc, and the organic phase was washed with water and saturated NaCl and then dried and concentrated, leaving an off-white solid. The crude **22** was purified by flash chromatography (EtOAc/CH_2Cl_2, 10/90) to afford 0.62 g (55%) of a white solid: mp 161−162 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (br s, 1H), 7.72 (d, J = 2.4, 1H), 7.26 (d, J = 2.3, 1H), 4.10−3.60 (br d, 2H), 2.33 (s, 3H), 1.56 (s, 9H); MS 281 (MH^+). Anal.

Calcd for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.65; H, 5.75; N, 9.72.

4-tert-Butyl-7-nitro-1H-1,4-benzodiazepine-2,5-dione (26). To a cold (ice/methanol bath) solution of 90% HNO_3 was added portions of compound **1** (12.20 g, 52.6 mmol) via a solid addition funnel over ca. 30 min while maintaining the internal temperature between −5 and −10 °C. After the addition, stirring was continued at −5 °C for 2.5 h. The yellowish solution was then poured onto 350 mL of ice while stirring. The resultant solid was collected, washed with cold water, and then dried, leaving 9.63 g (66%) of a white solid. A small sample was purified by recrystallization (EtOH/H_2O): mp 236−237 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 10.83 (br s, 1H), 8.61 (d, J = 2.7, 1H), 8.06 (dd, J = 2.7, 8.7, 1H), 7.17 (d, J = 8.7, 1H), 3.80 (br s, 2H), 1.44 (s, 9H); MS 278 (MH^+). Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.29; H, 5.50; N, 15.07.

7-Amino-4-tert-butyl-1H-1,4-benzodiazepine-2,5-dione (27). A solution of compound **26** (31.0 g, 112 mmol) in 800 mL of EtOH/THF (1/1, v/v) was hydrogenated over 10% Pd−C (4.65 g, 15 wt %) in a Parr apparatus until hydrogen uptake ceased (ca. 45 min.). The catalyst was filtered from the mixture, and the filtrate was concentrated leaving a pink solid. Trituration of the solid in EtOAc/hexanes (1/3) afforded 23.9 g (87%) of a pink solid: mp 218−219 °C; ^{1}H NMR (DMSO-d_6) δ 9.96 (br s, 1H), 6.92 (d, J = 2.7, 1H), 6.74 (d, J = 8.5, 1H), 6.66 (dd, J = 2.5, 8.5, 1H), 5.12 (br s, 2H), 3.90−3.60 (s, 2H) 1.44 (s, 9H); MS 248 (MH^+). Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.14; H, 6.91; N, 16.87.

4-tert-Butyl-2,3,4,5-tetrahydro-2,5-dioxo-1H-1,4-benzodiazepine-7-carbonitrile (28). To a suspension of compound **27** (1.00 g, 4.05 mmol) in 2 N HCl (4.5 mL) cooled to 0 °C was added $NaNO_2$ (0.29 g, 4.25 mmol). After being stirred for 10 min, the resultant orange-brown heterogeneous mixture was treated with solid Na_2CO_3 until the pH was raised to ca. 7. In a separate flask, a mixture of CuCN (0.47 g, 5.26 mmol) and NaCN (0.40 g, 8.10 mmol) in H_2O (4 mL) and EtOAc (8 mL) was cooled to 0 °C. The diazonium salt prepared above was added by pipet to the second flask, and the reaction was stirred for 30 min at 0 °C, warmed to room temperature during 1 h, and then heated at reflux for 1 h. After removal of the solids, the crude reaction mixture was chromatographed (EtOAc/hexanes, 40/60) to afford 0.30 g (29%) of compound **28** as an off-white solid: mp 212−214 °C; ^{1}H NMR ($CDCl_3$) δ 9.46 (br s, 1H), 8.31 (d, J = 2.1, 1H), 7.68 (dd, J = 2.1, 8.4, 1H), 7.11 (d, J = 8.4, 1H), 3.94 (br s, 2H), 1.57 (s, 9H); MS 258 (MH^+). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 64.95; H, 5.70; N, 16.01.

4-tert-Butyl-7-chloro-1-methyl-1H-1,4-benzodiazepine-2,5-dione (29). A suspension of compound **2** (0.50 g, 1.90 mmol), K_2CO_3 (1.04 g, 7.50 mmol), and methyl iodide (0.23 mL, 3.70 mmol) in THF was heated at reflux for 90 h, filtered through diatomaceous earth, and concentrated to give a residue. Flash chromatography (EtOAc/hexanes, 33−50%) of the residue gave compound **29** as a clear oil in nearly quantitative yield: ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 2.5, 1H), 7.42 (dd, J = 2.6, 8.7, 1H), 7.09 (d, J = 8.7, 1H), 4.09 (d, J = 15.0, 1H), 3.74 (d, J = 15.0, 1H), 3.36 (s, 3H), 1.56 (s, 9H).

4-tert-Butyl-7-chloro-1-(p-methoxybenzyl)-1H-1,4-benzodiazepine-2,5-dione (30). To a suspension of NaH (0.45 g, 11.3 mmol) in DMF (50 mL) cooled to 0 °C was added a solution of compound **2** (2.74 g, 10.3 mmol) in DMF (10 mL). After the mixture was stirred for 30 min, a solution of *p*-methoxybenzyl chloride (1.93 g, 12.4 mmol) in DMF (5 mL) was added. The solution was stirred for 1 h at 0 °C and 3 h at room temperature. The reaction mixture was diluted with Et_2O and then washed with four portions of H_2O. The combined aqueous extracts were back-extracted with Et_2O, and the organic layers were dried and concentrated to afford a light brown residue. Flash chromatography (EtOAc/hexanes, 20/80) gave 3.53 g of a clear oil (89%) which solidified to a white waxy solid: mp 103−106 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 2.4, 1H), 7.30 (dd, J = 2.4, 8.7, 1H), 7.12 (d, J = 8.7, 1H), 7.02 (d, J = 8.4, 2H), 6.75 (d, J = 8.4, 2H), 5.22 (d, J = 9.3, 1H), 4.77 (d, J = 9.6, 1H), 4.11 (d, J = 15.3, 1H), 3.80 (d, J = 15.3, 1H), 3.71 (s, 3H), 1.52 (s, 9H); MS 387 (MH^+). Anal. Calcd for $C_{21}H_{23}ClN_2O_3$: C, 65.20; H, 5.99; N, 7.24. Found: C, 65.12; H, 6.07; N, 7.03.

4-tert-Butyl-7-ethyl-1H-1,4-benzodiazepine-2,5-dione (33). A solution of compound **31** (0.70 g, 2.71 mmol) in EtOH (20 mL) was hydrogenated over 5% Pt−C (0.14 g, 20 wt %) at 50 psi for 4 h. The catalyst was then filtered and washed with additional EtOH. Concentration of the filtrate gave 0.58 g (82%) of compound **33** as a white solid: mp 182−184 °C; ^{1}H NMR (DMSO-d_6) δ 10.33 (br s, 1H), 7.57 (br s, 1H), 7.29 (dd, J = 1.5, 8.4, 1H), 6.97 (d, J = 8.4, 1H), 3.76 (br s, 2H), 2.58 (q, J = 7.8, 2H), 1.45 (s, 9H) 1.15 (t, J = 7.5, 3H); MS 261 (MH^+). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.43; H, 7.30; N, 10.83.

Biology Section. *Herbicide Evaluation.* All of the compounds described above were evaluated in both pre- and postemergence herbicide assays. The comparative herbicidal efficacies are based upon evaluations including four dicotyledonous species: velvetleaf (*Abutilon theophrasti*), ragweed (*Ambrosia artemisiifolia*), lambsquarters (*Chenopodium album*), and morningglory (*Ipomoea* spp.), and one monocotyledonous species, green foxtail (*Setaria viridis*).

Preemergence Herbicide Tests. A Sassafras sandy loam soil containing 1.0% organic matter was placed in 26 × 52 × 6.5 cm plastic flats with plastic inserts containing 8 × 8 × 6 cm cells. On top of the soil was placed a predetermined number of seeds of each of several monocotyledonous and dicotyledonous annual plant species. Each cell was then covered with 1 cm of soil. A known amount of test compound was dissolved in 50% acetone/water and applied directly to the soil surface. The amount of herbicide applied equaled 0.032, 0.063, 0.125, 0.250, 0.500, and 1.000 kg/ha. Tests were nonreplicated with herbicide treatments applied with a laboratory belt sprayer calibrated to deliver 400 L/ha. A 65015E nozzle was utilized for these tests, with a spray pressure of 275 kPa. After treatment, the flats were placed in a greenhouse and immediately watered overhead; subsequent watering was also overhead. Visual ratings of weed control were made approximately 3 weeks after treatment (WAT). Results of the greenhouse herbicide evaluation were expressed on a 0−9 rating scale. The scale is based on a visual observation of plant stand, vigor, malformation, size, and overall plant appearance as compared to an untreated control. In this scale, 0 represents no injury and 9 represents complete kill.

Postemergence Herbicide Tests. Tests were prepared in a manner identical to the preemergence tests except the growing media was Metro-Mix 350, a commercial potting mix, containing no mineral soil. After the weeds had reached the two-leaf stage (approximately 10 days), the plants were treated with the test compound dissolved in 50% acetone/water containing 0.25% (v/v) nonionic surfactant. The spray chamber settings and application rates were identical to those of the preemergence treatments. After spraying, the plants were returned to the greenhouse and not watered overhead for 72 h. During these 3 days water was applied directly to the soil surface. Injury and weed control ratings were taken 2 WAT. The rating scale was the same as for the preemergence tests.

In Vitro Photosystem II Assay. Isolation of chloroplasts. Chloroplasts were isolated from 6−10 week old spinach leaves according to the published methods (Shimuzu et al., 1988). The chloroplast suspension was stored at −80 °C to preserve the PS II activity.

Chlorophyll Determination. The amount of chlorophyll present in the chlorophyll/glycerol suspension was evaluated according to the published methods (MacKinney, 1941). The absorbance of the solution was measured with a Samsung Uvicon spectrophotometer. The exact amount of chlorophyll in the extract was calculated using the following equations:

$$(20.2)A_{645} + (8.02)A_{663} = \text{concentration of chlorophyll (mg/mL)}$$

$$\text{or } (28.9)A_{652} = \text{concentration of chlorophyll (mg/mL)}$$

where A signifies absorbance at the specified wavelength.

Photosystem II Assay. The Hill reaction (Shimuzu et al., 1988) was adapted to the microtiter plate format to accommodate a large number of test compounds. The chlorophyll suspension used in the reaction was diluted to the concentration of 1 mg/mL in the reaction buffer containing 50 mM Tris, pH 7.5. The substrate buffer contained 5 mM ferricyanide dissolved in Tris buffer. The stock solutions of the inhibitors were prepared with DMSO. The chlorophyll suspension, substrate buffer, and the test compounds were added to the microtiter plate wells and incubated at room temperature under strong light (ca. 27 000 lx) for 30 min. The reaction was stopped by the addition of trichloroacetic acid to a final concentration of 3%. Denatured proteins and membranes were collected on the bottom of the plate by centrifugation at 2000*g* for 5 min, and the absorbance of the supernatant was read at 420 nm. The photosystem II activity was measured by monitoring the absorbance decrease as ferricyanide was converted to ferrocyanide. An absorbance change rate corresponded to the activity of the tested inhibitors. The photosystem II activity of the compounds was expressed as the concentration of compound needed to cause 50% inhibition.

RESULTS AND DISCUSSION

Synthesis. The synthesis of benzodiazepinediones **1**−**21** (Table 1) is depicted in Scheme 1. In a number of examples where the requisite *o*-nitrobenzoyl chloride was not readily available, we chose to prepare the desired targets via further substitution of the benzodiazepinedione ring. Halogenation of the unsubstituted benzodiazepinedione **1** can be directed selectively to C-7, affording either the 7-bromo analogue **23** or the 7-iodo analogue **24** (Karp, 1995). When C-7 is already substituted, for example, with the chloro group of compound **2**, bromination can then be directed to C-9, affording the 7-chloro-9-bromo analogue **25** (Scheme 2). Chlorination (Adams and Gordon, 1950) of the 9-methyl analogue **15** gave, as expected, the 7-chloro-9-methyl analogue **22** as the major product. In addition, a small amount of product arising from benzylic chlorination of the 9-methyl group in addition to ring chlorination at C-7 was observed.

More complex benzenoid substitution could be effected via palladium-mediated coupling of the bromo- and iodobenzodiazepinedione analogues with alkenes and alkynes (Karp, 1995). Treatment of (trimethylsilyl)-acetylene with benzodiazepinediones **24**, **21**, and **25** in the presence of palladium(II) and Cu(I) gave a series of (trimethylsilyl)acetylene-substituted benzodiazepinediones which were hydrolyzed under basic conditions to the free acetylenes **32**, **35**, and **34** (Scheme 3). Treatment of compound **24** with vinyltrimethylsilane in the presence of palladium(II) gave a mixture of three vinyl-containing analogues, of which the 7-vinyl analogue **31** was the major component. Catalytic reduction of **31** gave the 7-ethyl analogue **33**.

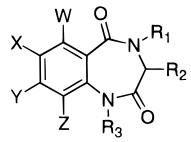
The preference for electrophilic attack at C-7 can be used to prepare other functionalized benzodiazepinediones (Scheme 4). Nitration of benzodiazepinedione **1** gave exclusively the 7-nitro analogue **26**. Reduction of the nitro group via catalytic hydrogenation afforded the 7-amino analogue **27**. Compound **27** was converted to the 7-cyano analogue **28** via the intermediate diazonium salt (Marburg and Tolman, 1980).

Substitution at the benzodiazepinedione N-1 position could be readily accomplished as demonstrated by the treatment of compound **2** with the appropriate electrophile under basic conditions. In this manner, the *N*-methyl and *N*-*p*-methoxybenzyl analogues **29** and **30**, respectively, were prepared.

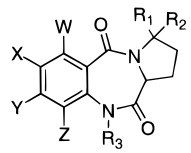
Herbicidal Activity. The comparative herbicidal activity of the target compounds was measured at the whole plant level via a greenhouse assay. In general, compounds exhibiting herbicidal activity were active both pre- and postemergence but were more phytotoxic to broadleaf weeds than the representative grass weed, green foxtail (*Setaria viridis*, Table 2). In general, lambsquarters (*C. album*) proved to be the most sensitive species. The more active compounds showed the typical chlorotic symptomology of photosynthesis inhibitors. As a measure of the in vitro activity of these compounds, I_{50} values for PSII inhibition in isolated spinach chloroplasts were determined (Table 3). The range of activity between the most and least active compounds was greater than 5000-fold. In general, the most active compounds in the greenhouse were also the most active in vitro, although there were exceptions. To adequately probe the structure−activity effect of these compounds, a variety of substituent modifications were made to the benzodiazepinedione nucleus including variation of substituents at all four benzenoid positions (C-6 to C-9) and variation in the diazepine ring (N-1, C-3, and N-4).

Substituent modification at C-3 and N-4 was initially investigated. As an early lead compound, pyrroloben-

Table 1. Structures of Benzodiazepinediones

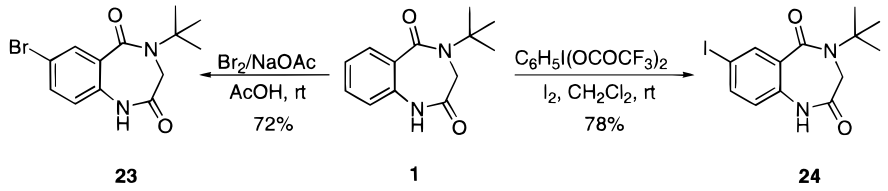


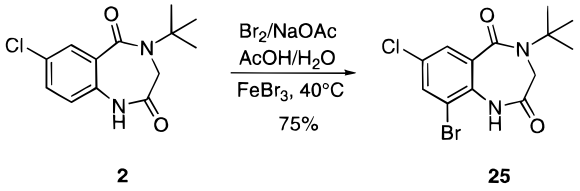
compd	W	X	Y	Z	R_1	R_2	R_3
1	H	H	H	H	*t*-Bu	H	H
2	H	Cl	H	H	*t*-Bu	H	H
3	H	Cl	H	H	*i*-Pr	H	H
4	H	Cl	H	H	neopentyl	H	H
5	H	Cl	H	H	neopentyl	Me	H
6	H	Cl	H	H	cyclopentyl	H	H
7	H	Cl	H	H	cyclobutyl	H	H
8	H	Cl	H	H	cyclopropyl	H	H
9	H	Cl	H	H	allyl	H	H
10	H	Cl	H	H	propargyl	H	H
11	H	Cl	H	H	furfuryl	H	H
12	H	Cl	H	H	3,5-$(F)_2C_6H_3$	H	H
13	H	Cl	H	H	3-$(CF_3)C_6H_4$	H	H
14	H	Cl	H	H	4-$(MeO)C_6H_4$	H	H
15	H	H	H	Me	*t*-Bu	H	H
16	H	Me	H	H	*t*-Bu	H	H
17	Me	H	H	H	*t*-Bu	H	H
18	H	OMe	H	H	*t*-Bu	H	H
19	H	Me	H	Me	*t*-Bu	H	H
20	H	F	H	H	*t*-Bu	H	H
21	H	H	Br	H	*t*-Bu	H	H
22	H	Cl	H	Me	*t*-Bu	H	H
23	H	Br	H	H	*t*-Bu	H	H
24	H	I	H	H	*t*-Bu	H	H
25	H	Cl	H	Br	*t*-Bu	H	H
26	H	NO_2	H	H	*t*-Bu	H	H
27	H	NH_2	H	H	*t*-Bu	H	H
28	H	CN	H	H	*t*-Bu	H	H
29	H	Cl	H	H	*t*-Bu	H	Me
30	H	Cl	H	H	*t*-Bu	H	PMB
31	H	vinyl	H	H	*t*-Bu	H	H
32	H	ethynyl	H	H	*t*-Bu	H	H
33	H	Et	H	H	*t*-Bu	H	H
34	H	Cl	H	ethynyl	*t*-Bu	H	H
35	H	H	ethynyl	H	*t*-Bu	H	H

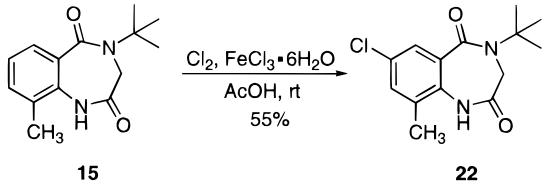


36	H	Cl	H	H	Me	Me	H
37	H	Cl	H	H	Me	H	H

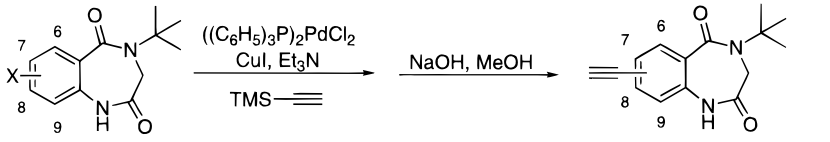
Scheme 2. Halogenation Reactions of Benzodiazepinediones



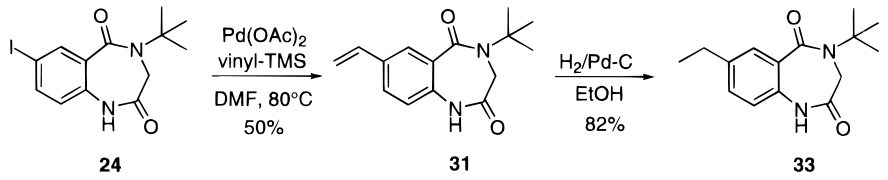




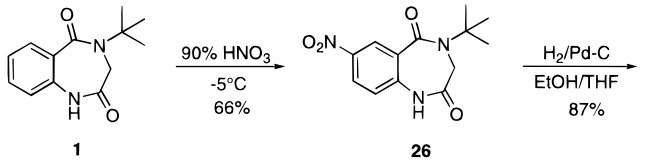
Scheme 3

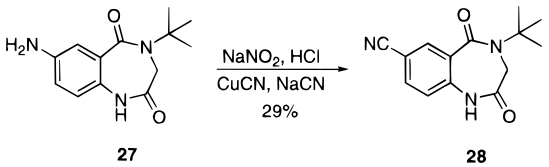


24 X=7-I	58%	85%	**32** X=7-ethynyl
21 X=8-Br	41%	86%	**35** X=8-ethynyl
25 X=7-Cl, 9-Br	72%	67%	**34** X=7-Cl, 9-ethynyl



Scheme 4





zodiazepinedione **36** was found to possess good preemergence and moderate postemergence activity. It was questioned whether the C-ring of pyrrolobenzodiazepinediones such as **36** and **37** was necessary for herbicidal activity. A variety of *N*-4-substituted analogues devoid of the C-ring were prepared. The most active analogue, compound **2**, containing an *N*-*tert*-butyl group, exhibited greater activity on broadleaf weeds both pre- and postemergence compared to compounds **36** and **37**. In addition, compound **2** demonstrated surprisingly good foxtail control preemergence. In the in vitro assay, compounds **2** and **37** exhibited comparable activity (I_{50} = 1.7 vs 1.9 μM) while **2** was approximately 1 order of magnitude more active than compound **36** (16.9 μM). The *N*-neopentyl analogue **4** was less active than the *N*-*tert*-butyl compound **2** both pre- and postemergence but was nearly 1 order of magnitude more active in vitro (I_{50} = 0.2 μM vs 1.7 μM). As the steric bulk at N-4 was decreased further, e.g., furfural (**11**), allyl (**9**), and propargyl (**10**), the greenhouse activity decreased markedly. With the exception of compound **11**, in vitro activity dropped off similarly. To further probe the effect of substitution at N-4, a series of cycloalkyl-substituted compounds were prepared, including cyclopentyl (**6**), cyclobutyl (**7**), and cyclopropyl (**8**). Of the three, the *N*-cyclobutyl analogue **7** was the most active in the greenhouse and was one of the few compounds showing greater activity postemergence than preemergence. All of the cycloalkyl analogues showed comparable in vitro activity (I_{50} =

Table 2. Pre- and Postemergence Herbicidal Activity of Substituted Benzodiazepinediones against Representative Weed Species[a]

	control rate, g/ha[b]									
	preemergence					postemergence				
compd	VL	RW	LQ	MG	FX	VL	RW	LQ	MG	FX
1	1000	500	250	500	>1000	500	>1000	125	>1000	i
2	125	125	63	125	250	500	500	250	250	1000
3	1000	1000	1000	1000	i	>1000	>1000	250	>1000	i
4	1000	1000	63	250	>1000	>1000	1000	63	>1000	>1000
5	i	i	i	i	i	i	i	i	i	i
6	1000	>1000	1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
7	500	500	250	>1000	>1000	250	>1000	125	>1000	i
8	>1000	>1000	1000	>1000	>1000	i	>1000	>1000	>1000	i
9	>1000	>1000	>1000	>1000	i	i	i	>1000	>1000	i
10	>1000	>1000	>1000	>1000	i	i	>1000	>1000	>1000	i
11	i	i	i	i	i	i	i	i	i	i
12	i	i	i	i	i	i	i	i	i	i
13	i	i	i	i	i	i	i	>1000	>1000	i
14	i	i	i	i	i	i	i	i	i	i
15	250	1000	250	500	>1000	500	>1000	125	1000	>1000
16	125	500	125	250	1000	500	1000	500	500	>1000
17	i	i	i	i	i	i	i	i	i	i
18	1000	>1000	250	>1000	i	1000	>1000	250	>1000	i
19	1000	1000	500	250	500	1000	>1000	500	500	1000
20	1000	1000	1000	1000	>1000	>1000	>1000	>1000	i	i
21	i	i	i	i	i	i	i	i	i	i
22	1000	1000	250	500	1000	>1000	>1000	250	500	1000
23	500	500	250	500	1000	250	1000	500	1000	1000
24	i	i	i	i	i	>1000	>1000	1000	i	>1000
25	i	i	i	i	i	i	i	i	i	i
26	i	i	i	i	i	i	i	i	i	i
27	i	i	i	i	i	i	i	i	i	i
28	i	i	i	i	i	i	i	i	i	i
29	>1000	>1000	125	1000	>1000	>1000	>1000	*c*	>1000	1000
30	i	i	i	i	i	i	i	i	i	i
31	i	i	i	i	i	i	i	i	i	i
32	1000	>1000	500	500	1000	>1000	>1000	1000	1000	>1000
33	i	i	i	i	i	i	i	i	i	i
34	i	i	i	i	i	i	i	i	i	i
35	i	i	i	i	i	i	i	i	i	i
36	500	500	63	500	1000	1000	1000	250	1000	1000
37	500	>1000	500	1000	>1000	>1000	>1000	500	>1000	>1000

[a] Key to the weed species in this study: VL, velvetleaf (*A. theophrasti*); RW, ragweed (*A. artemisiifolia*); LQ, lambsquarters (*C. album*); MG, morningglory (*Ipomoea* spp.); FX, green foxtail (*S. viridis*). [b] Application rate effecting >90% control of the targeted weed species. A ">" means that compound caused injury at given rate but did not control the target weed. An "i" denotes compound caused no injury to the target weed at the highest rate tested (1000 g/ha). [c] No data.

10−16 μM). To assess the effect of aryl substitution at N-4, a small set of phenyl-substituted analogues were prepared. Substitution at N-4 with 3,5-difluorophenyl (**12**), 3-trifluoromethylphenyl (**13**), or 4-methoxyphenyl (**14**) gave compounds that were completely devoid of herbicidal activity at the highest rate tested (1 kg/ha). With the exception of compound **13**, the *N*-aryl analogues had poor in vitro activity as well.

Herbicidal activity was surprisingly very sensitive to substitution at C-3 in the bicyclic series. Substitution of the *N*-neopentyl analogue **4** with a C-3 methyl group (to give **5**) caused a complete loss of herbicidal activity. In addition, the in vitro PSII activity dropped more than 2000-fold (from I_{50} = 0.2 to 437 μM). This would appear surprising since the pyrrolobenzodiazepinediones **36** and **37**, which, due to the fused pyrrolidine ring contain branching at this same carbon atom, possess moderate to good activity both at the whole plant level and in vitro. A plausible explanation might be that in the bicyclic series, any substituents present at C-3 and N-4 would tend to maximize their distance from each other so as to avoid sterically unfavorable eclipsing interactions. In the pyrrolobenzodiazepinediones, the eclipsing interactions cannot be avoided. Although we found that increasing steric bulk at N-4 was favorable for herbicidal activity, apparently additional bulk at C-3 causes a detrimental effect . Despite numerous attempts, the C-3 methyl analogue of **2** could not be prepared. From this we infer that steric bulk is playing an important role.

Next, the effect of substitution at N-1 on herbicidal activity was studied. Substitution of compound **2** with *N*-methyl (**29**) caused a significant drop in herbicidal activity both pre- and postemergence. Substitution by *p*-methoxybenzyl (**30**) caused complete loss of herbicidal activity. A similar decrease in in vitro activity was observed as well.

Third, we investigated the effect of substitution in the benzene ring (C-6 to C-9) on herbicidal activity. For the following comparisons the *N*-4-*tert*-butyl group was held constant. A series of isomeric benzodiazepinediones containing a methyl substituent at C-9, C-7, and C-6 were prepared for evaluation (**15**, **16**, and **17**, respectively). As the results in Tables 2 and 3 demonstrate, the 7-methyl analogue **16** was the most active both pre- and postemergence followed by the 9-methyl analogue **15**. The 6-methyl analogue **17** was completely devoid of activity at the highest rate tested. A similar trend was observed in vitro. Due to the level of activity observed for compounds **15** and **16**, other 7- and 9-substituted compounds were prepared and evaluated. The 7-methoxy analogue **18** was less active than either the 7-chloro (**2**) or 7-methyl (**16**) compounds. The 7-amino compound (**27**) was inactive at the highest rate tested as were compounds containing electron-with-

Table 3. Photosystem II I_{50} Values from Isolated Spinach Chloroplasts

compd	PSII I_{50}, mM
1	13.8
2	1.7
3	60
4	0.2
5	437
6	15
7	9.6
8	16
9	198
10	295
11	2.1
12	310
13	4
14	>1000
15	3.3
16	1.7
17	>1000
18	39
19	4.1
20	500
21	532
22	1.3
23	0.5
24	4.6
25	>1000
26	>1000
27	600
28	582
29	518
30	>1000
31	54
32	1.6
33	151
34	>1000
35	>1000
36	16.9
37	1.9

drawing groups at C-7, e.g., nitro (**26**) and cyano (**28**). The high level of activity of the 7-chloro analogue **2** prompted the preparation and evaluation of other 7-halogenated analogues. In this series herbicidal activity decreased in the order 7-Cl (**2**) > 7-Br (**23**) > 7-F (**20**) > 7-I (**24**). While **23** was less active than **2** in the greenhouse, it was somewhat more potent in vitro. Interestingly, compound **20** was a much poorer PSII inhibitor than compound **24** (I_{50} = 500 vs 4.6 μM, respectively). Obviously, the whole plant activity is a reflection of not only the inherent activity of the compounds (in vitro), but of uptake, translocation, and metabolic effects as well. A compound such as **20** may be exerting its herbicidal activity by a mechanism other than PSII, while the high in vitro/low whole plant activity of compound **24** may be due to the lack of the requisite physicochemical characteristics.

To further probe the structure−activity relationship, additional halogenated analogues were prepared. The 8-bromo analogue (**21**) was devoid of herbicidal activity at the highest rate tested. Introduction of a bromine substituent at C-9 (**25**) caused a complete loss of herbicidal activity compared to **2**. However, when C-9 was substituted with a methyl group (**22**), only a small drop in whole plant activity was observed as compared to compound **2**. Further evidence that a methyl substituent is tolerated at the 9-position was demonstrated by the 7,9-dimethyl analogue **19**. Only a small decrease in activity is observed as compared to the 7-methyl analogue **16**.

Introduction of ethyl, vinyl, and ethynyl moieties into the various benzenoid positions could be effected from the halogenated benzodiazepinediones **21**, **24**, and **25**. As compared to the 7-methyl analogue **16**, substitution of C-7 with two-carbon fragments (varying in the degree of saturation) afforded lesser active compounds. The 7-ethynyl analogue **32** exhibited moderate whole plant activity, while the 7-vinyl (**31**) and 7-ethyl (**33**) derivatives were devoid of herbicidal activity at the highest rate tested. Compounds **16** and **32** were of comparable activity in vitro (1.7 μM vs 1.6 μM), while **31** and **33** were 30−100 times less potent. Introduction of an ethynyl moiety at either C-8 (**35**) or C-9 (**34**) resulted in inactive compounds.

CONCLUSION

The results of these studies have demonstrated the herbicidal activity of benzodiazepinediones. The structure−activity requirements of these compounds demonstrate that a rather narrow range of substitution is tolerated. Substitution at N-1 and C-3 (in the bicyclic series) causes a detrimental effect on the herbicidal activity in the presence of a bulky substituent at N-4 as does benzenoid substitution at C-6 and C-8. Substitution at N-4 was tolerated well with bulky substituents with *tert*-butyl conferring the highest level of activity. In the aromatic portion of the molecule, substitution at C-7 with chloro, bromo, and methyl and at C-9 with methyl afforded the most active compounds.

ABBREVIATIONS USED

PMB, *para*-methoxybenzyl; VL, velvetleaf; RW, ragweed; LQ, lambsquarters; MG, morningglory species; FX, green foxtail; I_{50}, concentration of compound causing 50% inhibition.

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