Synthesis and Herbicidal Activity of *N*-Oxide Derivatives

Hugo Cerecetto,* Eduardo Dias, Rossanna Di Maio, Mercedes González,* Sandra Pacce, Patricia Saenz, and Gustavo Seoane

Cátedra de Química Orgánica, Facultad de Química, Universidad de la República, CC 1157, 11800 Montevideo, Uruguay

Leopoldo Suescun and Alvaro Mombrú

Laboratorio de Cristalografía y Química del Estado Sólido, Facultad de Química, Universidad de la República, Montevideo, Uruguay

Grisel Fernández, Marisa Lema, and Juana Villalba

Cátedra de Cereales y Cultivos Industriales, Facultad de Agronomía, Universidad de la República, Paysandú, Uruguay

As part of an ongoing program on the chemistry and biological activity of *N*-oxide-containing molecules, a number of novel 1,2,5-oxadiazole *N*-oxide, benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide, and quinoxaline *N*,*N*′-dioxide derivatives were synthesized and evaluated for their herbicidal activity. Many of these compounds exhibited moderate to good herbicidal pre-emergence activity against *Triticum aestivum*. Dose−response studies were done on the more representative compounds (**12**, **20**, and **26**). The most active compound, butylcarbamoylbenzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide, **26**, displayed herbicidal activity at concentrations as low as 24 g/ha.

Keywords: *Herbicide; 1,2,5-oxadiazole N-oxide; benzo[1,2-c]1,2,5-oxadiazole N-oxide; quinoxaline N,N′-dioxide*

INTRODUCTION

The discovery and development of new herbicides is a long and difficult endeavor. A large number of herbicides are currently available to assist in controlling weeds in a variety of crops. Herbicides can be classified into families based on their chemical structures and modes of action (Thedoridis et al., 1990, and references therein). For example, the pyrazole phenyl ether herbicides act by inhibiting the protoporphyrinogen oxidase (Clark, 1996; Nandihalli et al., 1994); the sulfonylureas and imidazolinones inhibit amino acid biosynthesis (Kleschick et al., 1990, and references therein; Wepplo, 1990; Hay, 1990); and the bipyridinium herbicides (Baker and Percival, 1990) act by competing for electrons with the natural substrate ferredoxin.

In the course of our work on *N*-oxide derivatives (Monge et al., 1998a; Cerecetto et al., 1999), we developed a number of compounds that combined in a single structure several features of the toxophores described above. Consequently, they contain a quaternary nitrogen (as the bipyridinium family) and a heterocyclic system structurally related to the other families (pyrazole phenyl ethers, sulfonylureas, and imidazolinones) (see Chart 1). On the other hand, several groups have investigated the mechanism responsible for the biological activity of the *N*-oxide system and have found that the toxic species is an oxidizing radical (Cahill and White, 1991; Monge et al., 1995, 1998b). Therefore, it occurred to us to examine the herbicidal activity of new *N*-oxide-containing compounds developed in our laboratory.

In this paper we report on the synthesis of *N*-oxide compounds derived from 1,2,5-oxadiazole, benzo[1,2-*c*]1,2,5-oxadiazole, and quinoxaline heterocycles. The syntheses and structures of the *N*-oxide derivatives described here (**1**−**34**) are presented in Schemes 1−3. All new compounds were identified by ^{1}H NMR and, in some cases, by ^{13}C NMR, IR, and MS. Their purity was established by TLC and microanalysis. The herbicidal activity of these compounds was examined through a preliminary screening program in both pre- and post-emergence assays (using *Triticum aestivum* L. as biological species). Dose−response studies were performed with the more representative products of each family of compounds.

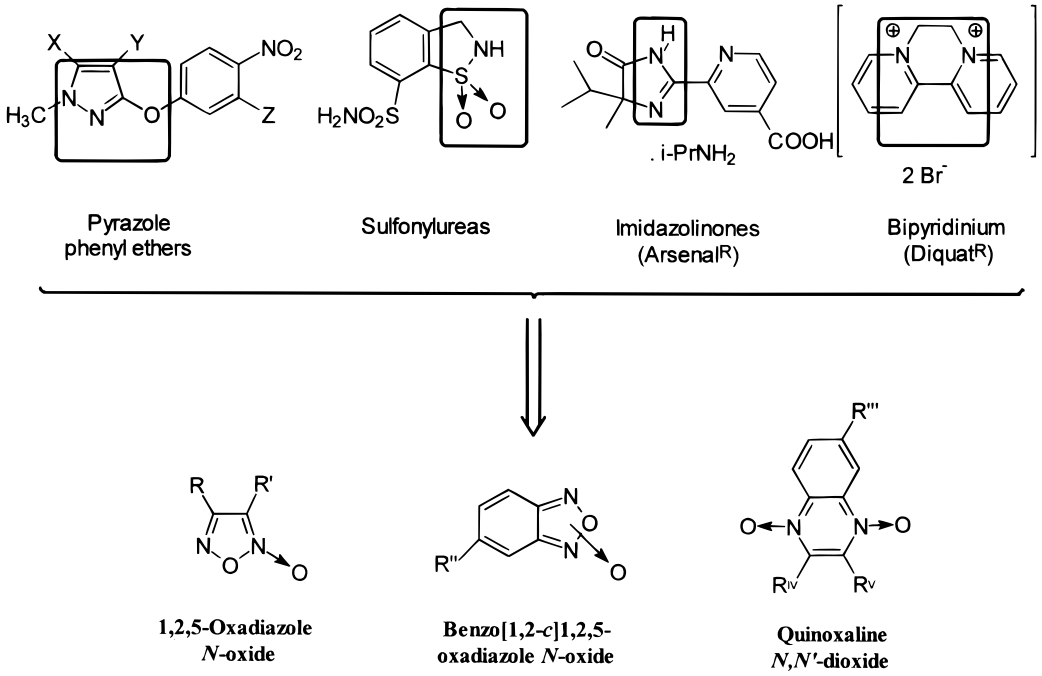
MATERIALS AND METHODS

Chemistry. Synthetic Methods. All starting materials were commercially available research-grade chemicals and used without further purification. Compounds **1**−**18**, **26**, and **33** and intermediates **I**−**IX** and **XI**−**XIV** were prepared according to procedures found in the literature (Gasco et al., 1991; Monge et al., 1995, 1998a; Fruttero et al., 1989; Smith and Boyer, 1963; Edwards and Bambury, 1975; Cerecetto et al., 1998, 1999). All solvents were dried and distilled prior to use (Perrin and Armarego, 1988). All reactions were carried out in a nitrogen atmosphere. The typical workup included washing with brine and drying the organic layer with Na_2SO_4. Melting points were determined using a Leitz microscope heating stage model 350 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples

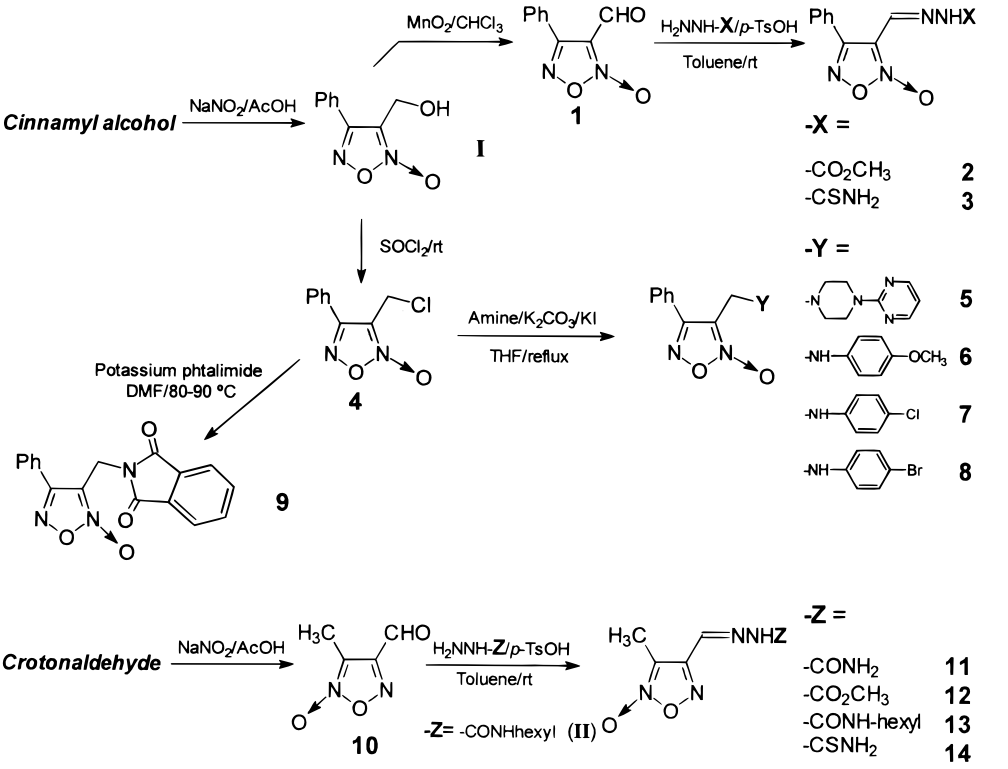
* Authors to whom correspondence should be addressed [(H.C.) fax (598) 2 924 19 06, e-mail hcerecet@bilbo.edu.uy; (M.G.) fax (598) 2 924 19 06, e-mail megonzal@bilbo.edu.uy].

10.1021/jf9904766 CCC: $19.00
Published on Web 06/13/2000

Chart 1



Scheme 1

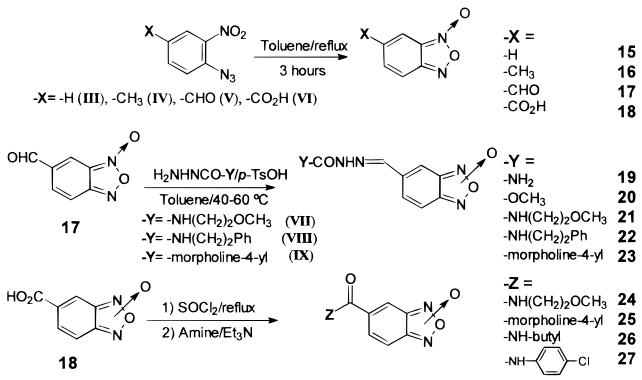


(over phosphorus pentaoxide at 3−4 mmHg, 24 h at room temperature) and performed on a Fisons EA 1108 CHNS-O analyzer and were within ±0.4% of theoretical values. Infrared spectra were recorded on a Perkin-Elmer 1310 instrument, using potassium bromide tablets for solid and oil products; the frequencies are expressed in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-100 (at 100 MHz) instrument or on a DPX-Bruker 400 (at 400 and 100 MHz) instrument, with tetramethylsilane as the internal reference and in the indicated solvent; the chemical shifts are reported in parts per million. Mass spectra were recorded on a Shimadzu GC-MS QP 1100 EX instrument at 70 eV.

Preparation of Semicarbazones 19−23. *General Procedure.* A mixture of **17** (1 equiv), semicarbazide (hydrochloride semicarbazide, methyl carbazate, **VII**, **VIII**, or **IX**) (1 equiv), *p*-TsOH (catalytic amounts), and toluene as solvent was stirred at 40−60 °C until the carbonyl compound was not present (followed by TLC on SiO_2, 1% MeOH in CH_2Cl_2). After the workup process, the residue was purified as indicated.

*1-[(Benzo[1,2-c]1,2,5-oxadiazol-5(6)-yl N_1-oxide)methylidene]-semicarbazide, (**19**),* was purified by column chromatography [SiO_2, EtOAc/MeOH (0−10%)] and then crystallized from MeOH, yellow needles (30%): mp 215.0−218.0 °C; IR ν_{max} 3410, 3250, 1650, 1570, 1050 cm^{-1}; ^1H NMR (DMSO-d_6, 100

Scheme 2



MHz) δ 6.60 (bs, 2H), 7.65 (d, J = 9.0 Hz, 0.4H), 7.70 (d, J = 8.0 Hz, 0.6H), 7.80 (d, J = 1.0 Hz, 0.4H), 7.85 (s, 0.6H), 7.89 (s, 0.4H), 8.00 (dd, J_1 = 1.0 Hz, J_2 = 8.0 Hz, 0.6H), 8.20 (dd, J_1 = 1.0 Hz, J_2 = 9.0 Hz, 0.4H), 8.49 (d, J = 1.0 Hz, 0.6H), 10.50 (bs, 0.4H), 10.68 (bs, 0.6H); MS, *m/z* (abundance) 221 ($M^{+\bullet}$, 28.1%), 205 (3.6%). Anal. Calcd for $C_8H_7N_5O_3 \cdot {}^1/_3H_2O$: C, 42.29; H, 3.38; N, 30.84. Found: C, 42.59; H, 3.00; N, 30.74.

*2′-[(Benzo[1,2-c]1,2,5-oxadiazol-5(6)-yl N_1-oxide)methylidene]-1-methoxymethanehydrazide, (**20**),* was purified by crystallization from toluene, yellow amorphous solid (73%): mp 208.0−210.0 °C; IR ν_{max} 3220, 3100, 2960, 1705, 1165 cm^{-1}; ^1H NMR (DMSO-d_6, 100 MHz) δ 3.82 (s, 3H), 7.80 (d, J = 6.0 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.96 (dd, J_1 = 2.0 Hz, J_2 = 6.0 Hz, 1H), 8.10 (s, 1H), 10.50 (bs, 1H); MS, *m/z* (abundance) 236 ($M^{+\bullet}$, 40.8%), 220 (1.2%). Anal. Calcd for $C_9H_8N_4O_4 \cdot {}^1/_2H_2O$: C, 44.08; H, 3.67; N, 22.86. Found: C, 44.23; H, 3.34; N, 22.56.

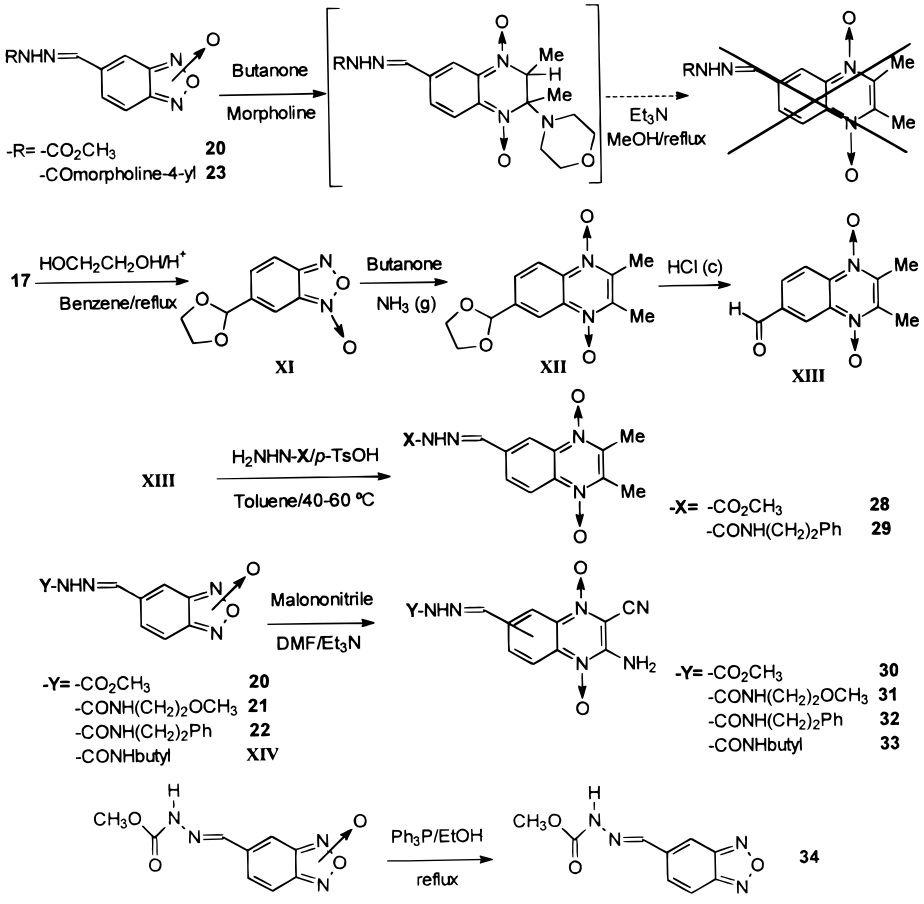
*1-[(Benzo[1,2-c]1,2,5-oxadiazol-5(6)-yl N_1-oxide)methylidene]-4-(2-methoxyethyl)semicarbazide, (**21**),* was purified by crystallization from EtOH/MeOH, yellow needles (52%): mp 223.0−224.0 °C; IR ν_{max} 3400, 3080, 2930, 1670, 1610, 1390 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.27 (s, 3H), 3.32 (q, J = 6.0 Hz, 2H), 3.43 (t, J = 6.3 Hz, 2H), 7.33 (t, J = 5.8 Hz, 1H), 7.50−7.85 (m, 2H), 7.90 (s, 1H), 8.00−8.30 (m, 1H), 10.79 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 38.57, 57.79, 70.97, 110.40, 112.40, 114.40, 115.60, 117.61, 127.65, 131.20, 136.40, 136.78, 152.80, 155.08; MS, *m/z* (abundance) 279 ($M^{+\bullet}$, 2.0%), 178 (7.5%). Anal. Calcd for $C_{11}H_{13}N_5O_4$: C, 47.31;H, 4.66;N, 25.09. Found: C, 47.39; H, 4.64; N, 24.79.

*1-[(Benzo[1,2-c]1,2,5-oxadiazol-5(6)-yl N_1-oxide)methylidene]-4-(2-phenylethyl)semicarbazide, (**22**),* was purified by column chromatography [SiO_2, petroleum ether/EtOAc (30−90%)] and then crystallized from petroleum ether/EtOAc, yellow needles (55%): mp 201.0−203.0 °C; IR ν_{max} 3395, 3185, 3070, 2930, 1675, 1595, 1360 cm^{-1}; ^1H NMR (DMSO-d_6, 100 MHz) δ 2.82 (t, J = 7.0 Hz, 2H), 3.42 (q, J = 6.0 Hz, 2H), 7.25 (m, 6H), 7.60−8.50 (m, 4H), 10.80 (bs, 1H); MS, *m/z* (abundance) 325 ($M^{+\bullet}$, 1.0%), 309 (1.0%). Anal. Calcd for $C_{16}H_{15}N_5O_3$: C, 59.08; H, 4.62; N, 21.54. Found: C, 59.10; H, 4.53; N, 21.50.

*2′-[(Benzo[1,2-c]1,2,5-oxadiazol-5(6)-yl N_1-oxide)methylidene]-1-(morpholine-4-yl)methane hydrazide, (**23**),* was purified by column chromatography [SiO_2, EtOAc/MeOH (0−30%)] and then crystallized from MeOH/EtOH, bright red plates (48%): mp 234.0−237.0 °C; IR ν_{max} 3200, 3050, 2850, 1640, 1610, 1380, 1240, 1100 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.44 (m, 4H), 3.61 (m, 4H), 7.50−8.00 (m, 3H), 8.20 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.13, 65.82, 111.03, 113.10, 114.48, 115.86, 118.28, 127.24, 130.00, 139.31, 139.91, 152.76, 153.78; MS, *m/z* (abundance) 291 ($M^{+\cdot}$, 0.3%), 275 (0.2%). Anal. Calcd for $C_{12}H_{13}N_5O_4 \cdot {}^1/_2H_2O$: C, 48.00; H, 4.67; N, 23.33. Found: C, 48.39; H, 4.67; N, 22.93.

Preparation of Amides 24, 25, and 27. *General Procedure.* A mixture of **18** (1 equiv), $SOCl_2$ (10 equiv), and DMF (catalytic amounts) was heated at reflux for 3 h. The excess of $SOCl_2$ was eliminated by distillation at reduced pressure, and the residue was cooled to 0 °C. At this moment a mixture of

Scheme 3



amine (2-methoxyethylamine, morpholine, or 4-chloroaniline) (1 equiv), Et_3N (2 equiv), and dry CH_2Cl_2 was added, and the reaction was stirred at room temperature for 12 h. After the workup process, the residue was purified as indicated.

*5(6)-(2-Methoxyethyl)carbamoylbenzo[1,2-c]1,2,5-oxadiazole N_1-oxide, (**24**),* was purified by column chromatography [Al_2O_3, petroleum ether/EtOAc (0−30%)] and then crystallized from petroleum ether/EtOAc, yellow needles (30%): mp 115.5−116.0 °C; IR ν_{max} 3300, 3075, 2930, 2830, 1635, 1580, 1305 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.28 (s, 3H), 3.45 (t, J = 5.2 Hz, 2H), 3.47 (q, J = 4.8 Hz, 2H), 7.50−8.50 (m, 3H), 8.93 (bt, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 39.87, 57.80, 70.05, 112.71, 115.49, 116.20, 117.66, 128.20, 129.02, 131.32, 132.03, 137.74, 148.71, 148.95, 163.75, 164.41; MS, *m/z* (abundance) 237 ($M^{+\bullet}$, 10.1%), 205 (6.3%), 189 (31.2%). Anal. Calcd for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.65; N, 17.72. Found: C, 50.72; H, 4.63; N, 17.60.

*5(6)-(Morpholine-4-yl)carbamoylbenzo[1,2-c]1,2,5-oxadiazole N_1-oxide, (**25**),* was purified by column chromatography [Al_2O_3, petroleum ether/EtOAc (0−20%)] and then crystallized from petroleum ether/EtOAc, pale yellow needles (49%): mp 160.5−162.0 °C; IR ν_{max} 3080, 2910, 2850, 1615, 1585, 1525, 1250, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 3.50−3.90 (m, 8H), 7.35−8.00 (m, 3H); MS, *m/z* (abundance) 249 ($M^{+\cdot}$, 59.7%), 233 (6.0%). Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.42; N, 16.87. Found: C, 53.41; H, 4.57; N, 16.80.

*5(6)-(4-Chlorophenyl)carbamoylbenzo[1,2-c]1,2,5-oxadiazole N_1-oxide, (**27**),* was purified by column chromatography [Al_2O_3, CH_2Cl_2/MeOH (0−30%)] and then crystallized from DMF/H_2O, brownish yellow needles (34%): mp 231.5−233.5 °C; IR ν_{max} 3400, 3090, 3060, 1670, 1575, 1310, 835, 815 cm^{-1}; ^1H NMR (DMSO-d_6, 100 MHz) δ 7.43 (d, J = 9.0 Hz, 2H), 7.80 (m+d, 4H), 8.32 (s, 1H), 10.62 (bs, 1H); MS, *m/z* (abundance) 289 ($M^{+\bullet}$, 40.5%), 273 (9.1%). Anal. Calcd for $C_{13}H_8ClN_3O_3$: C, 53.89; H, 2.76; N, 14.51. Found: C, 53.68; H, 2.80; N, 14.53.

Preparation of Quinoxaline *N,N′*-Dioxides 28 and 29. *General Procedure.* A stirred mixture of **XIII** (1 equiv), semicarbazide (methyl carbazate or **VIII**) (1 equiv), *p*-TsOH (catalytic amounts), and toluene as solvent was heated at 40−60 °C until the carbonyl compound was no longer present (followed by TLC SiO_2, 1% MeOH in CH_2Cl_2). After the workup process, the residue was purified as indicated.

*2′-[(2,3-Dimethylquinoxalin-6-yl N_1,N_4-dioxide)methylidene]-1-methoxymethanehydrazide, (**28**),* was purified by crystallization from toluene, yellow solid (83%): mp >300.0 °C; IR ν_{max} 3570, 3490, 3190, 3050, 1720, 1565, 1310 cm^{-1}; ^1H NMR (DMSO-d_6, 100 MHz) δ 2.76 (s, 3H), 2.78 (s, 3H), 3.74 (s, 3H), 8.12 (s, 1H), 8.30 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 8.40 (d, J = 2.0 Hz, 1H), 8.78 (d, J = 8.0 Hz, 1H), 10.30 (bs, 1H); MS, *m/z* (abundance) 290 ($M^{+\bullet}$, 86.5%), 274 (47.2%), 257 (17.9%). Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.83; N, 19.31. Found: C, 53.50; H, 4.53; N, 19.49.

*1-[(2,3-Dimethylquinoxalin-6-yl N_1,N_4-dioxide)methylidene]-4-(2-phenylethyl)semicarbazide, (**29**),* was purified by crystallization from toluene, yellowish green solid (68%): mp 257.0−259.0 °C; IR ν_{max} 3400, 3330, 3220, 3080, 2920, 1670, 1525, 1315 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.61 (s, 3H), 2.64 (s, 3H), 2.84 (t, J = 8.0 Hz, 2H), 3.39 (q, J = 7.8 Hz, 2H), 7.28 (m, 6H), 8.08 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 10.69 (s, 1H); MS, *m/z* (abundance) 379 ($M^{+\bullet}$, 7.8%), 362 (3.0%), 346 (3.1%). Anal. Calcd for $C_{20}H_{21}N_5O_3$: C, 63.32; H, 5.54; N, 18.47. Found: C, 63.00; H, 5.53; N, 18.50.

Preparation of Quinoxaline *N,N′*-Dioxides 30−32. *General Procedure.* A mixture of benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide (**20**, **21**, or **22**) (1 equiv) and malononitrile (1.1 equiv) was stirred for 10 min at 0 °C. At this temperature a solution of Et_3N (1 drop) in DMF was added, and the mixture was allowed to stand at room temperature over 24 h and then filtered off. The solid product (**30**−**32**) was washed with Et_2O, boiling MeOH, boiling DMF, and boiling H_2O.

*2′-[(2(3)-Amino-3(2)-cyanoquinoxalin-6-yl N_1,N_4-dioxide)-methylidene]-1-methoxymethane hydrazide, (**30**),* was obtained as a red-orange solid (73%): mp (the mixture) > 300.0 °C; IR ν_{max} 3290, 3070, 2230, 1730, 1625, 1530, 1330,1230 cm^{-1}; ^1H NMR (DMSO-d_6/D_2O, 100 MHz) δ 3.75 (s, 3H), 7.87 (s, 0.4H), 8.10 (m, 1H), 8.16 (s, 0.6H), 8.20 (s, 0.4H), 8.25 (s, 0.6H), 8.32 (d, J = 11.0 Hz, 0.6H), 8.39 (d, J = 9.0 Hz, 0.4H); MS, *m/z* (abundance) 302 ($M^{+\bullet}$, 10.1%), 286 (25.5%), 213 (6.3%). Anal. Calcd for $C_{12}H_{10}N_6O_4\cdot H_2O$: C, 45.00; H, 3.75; N, 26.25. Found: C, 45.37; H, 3.87; N, 25.90.

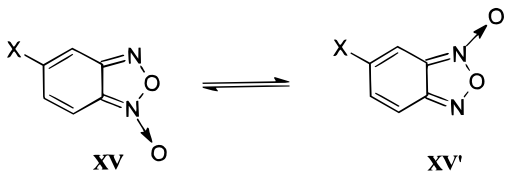


Figure 1. Isomeric forms of compounds **18**−**27** at room temperature (through NMR analysis).

*1-[(2(3)-Amino-3(2)-cyanoquinoxalin-6-yl N_1,N_4-dioxide)-methylidene]-4-(2-methoxyethyl) semicarbazide, (**31**),* was obtained as a red-brown solid (77%): mp (the mixture) > 300.0 °C; IR ν_{max} 3390, 3310, 3270, 2920, 2200, 1670, 1630, 1530, 1340, 1120 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.29 (s, 3H), 3.33 (q, J = 5.5 Hz, 2H), 3.43 (t, J = 6.1 Hz, 2H), 7.19 (t, J = 5.7 Hz, 0.5H), 7.23 (t, J = 5.5 Hz, 0.5H), 7.96 (s, 0.5H), 8.02 (s, 0.5H), 8.04 (d, J = 11.0 Hz, 0.5H), 8.08 (bs, 1H), 8.12 (bs, 1H), 8.23 (s, 1H), 8.26 (d, J = 9.0 Hz, 0.5H), 8.33 (d, J = 11.0 Hz, 0.5H), 8.47 (d, J = 9.1 Hz, 0.5H), 10.63 (s, 0.5H), 10.77 (s, 0.5H); MS, *m/z* (abundance) 345 ($M^{+\cdot}$, 0.5%), 329 (2.7%), 313 (2.6%). Anal. Calcd for $C_{14}H_{15}N_7O_4\cdot{}^1/_2H_2O$: C, 47.46; H, 4.52; N, 27.68. Found: C, 47.50; H, 4.50; N, 27.89.

*1-[(2(3)-Amino-3(2)-cyanoquinoxalin-6-yl N_1,N_4-dioxide)-methylidene]-4-(2-phenylethyl) semicarbazide, (**32**),* was obtained as a red solid (78%); mp (the mixture) > 300.0 °C; IR ν_{max} 3405, 3310, 3270, 2930, 2860, 2240, 1675, 1600, 1530, 1340 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.82 (t, J = 7.7 Hz, 2H), 3.40 (q, J = 6.4 Hz, 2H), 7.22−7.34 (m, 6H), 7.96 (s, 0.6H), 8.01 (s, 0.4H), 8.04 (d, J = 11.0 Hz, 0.6H), 8.09 (bs, 0.8H), 8.13 (bs, 1.2H), 8.22 (d, J = 9.1 Hz, 0.4H), 8.25 (s, 0.6H), 8.27 (s, 0.4H), 8.33 (d, J = 11.0 Hz, 0.6H), 8.44 (d, J = 9.3 Hz, 0.4H), 10.63 (s, 0.6H), 10.77 (s, 0.4H); MS, *m/z* (abundance) 391 ($M^{+\cdot}$, 0.2%), 375 (0.6%), 359 (1.6%). Anal. Calcd for $C_{19}H_{17}N_7O_3$: C, 58.31; H, 4.35; N, 25.06. Found: C, 58.52; H, 4.03; N, 25.30.

*2′-[(Benzo[1,2-c]1,2,5-oxadiazol-5-yl)methylidene]-1-methoxymethanehydrazide, (**34**).* A mixture of **20** (1 equiv), Ph_3P (1.1 equiv), and EtOH as solvent was heated at reflux for 1.5 h (Boyer and Ellzey, 1961). The EtOH was eliminated by distillation at reduced pressure. After the workup process, the residue was purified by column chromatography [SiO_2, CH_2Cl_2/MeOH (0−1%)] and then crystallized from MeOH, yellow needles (46%): mp 199.0−201.0 °C; IR ν_{max} 3250, 3200, 1746, 1694, 1238 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.74 (s, 3H), 8.04 (dd, J_1 = 1.2 Hz, J_2 = 9.5 Hz, 1H), 8.07 (d, J = 9.9 Hz, 1H), 8.17 (d, J = 1.0 Hz, 1H), 8.18 (s, 1H), 11.50 (bs, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 53.10, 116.32, 117.38, 130.33, 139.42, 142.00, 149.90, 150.12, 154.75; MS, *m/z* (abundance) 220 ($M^{+\bullet}$, 1.6%), 190 (0.1%), 189 (0.2%). Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09;H, 3.64;N, 25.45. Found: C, 49.38; H, 3.64; N, 25.27.

Biology. *Herbicide Evaluation.* The compounds described above were evaluated in pre-emergence herbicide assays. Some of them (**4**, **5**, **15**, and **18**) were also examined for their postemergence herbicidal activity. The preliminary herbicidal efficacies are based upon evaluations on *T. aestivum* L. Dose−response studies were done over compounds **12**, **20**, and **26**. All data were statistically analyzed (ANOVA), and the experiments were run in duplicate.

Pre-emergence Herbicide Tests. Sterilized sand was placed in 24 × 40 × 7 cm plastic flats with plastic inserts containing 8 × 8 × 6 cm cells (pH of the potting medium is near neutrality). On top of the sand in each cell was placed a predetermined number of seeds, which were then covered with 1 cm of additional sand. A known amount of test compound was dissolved or suspended and applied directly to the soil surface, using a laboratory belt sprayer calibrated to deliver ∼200 L/ha. One of the following carriers was employed as

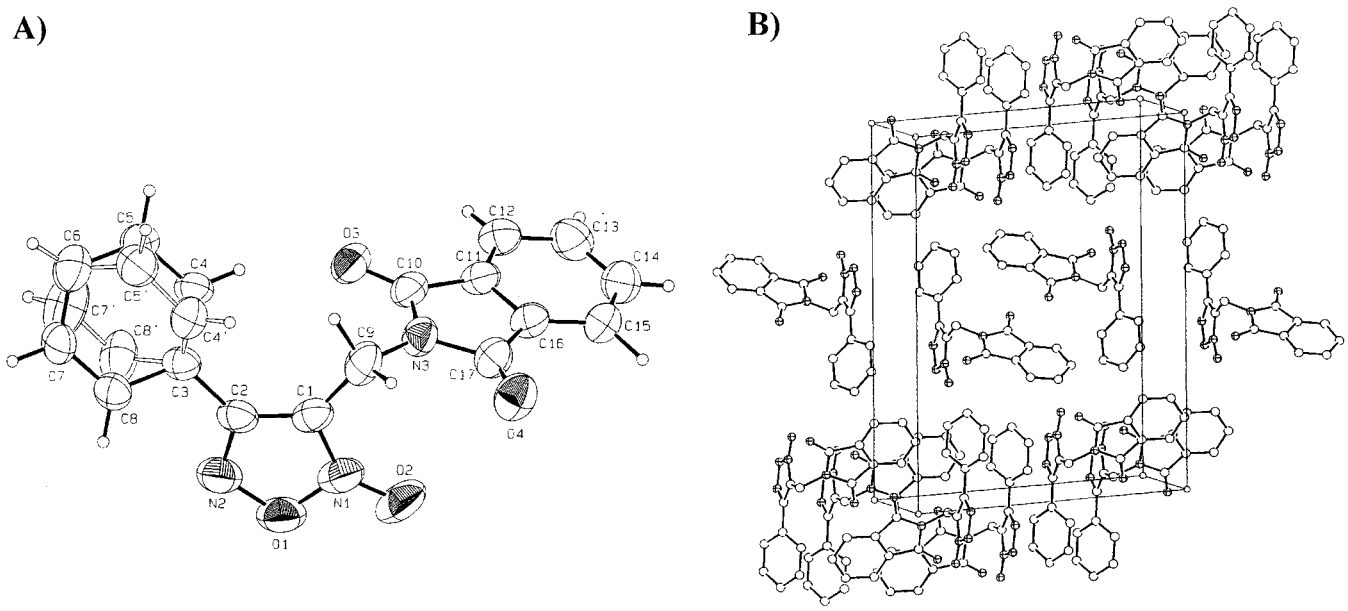


Figure 2. (A) ORTEP diagram of compound **9**; (B) packing diagram of compound **9** with unit cell. Both diagrams were generated with the XZORW package (Zsolnai and Pritzkow, 1995).

vehicle for each tested compound: acetone/H_2O, 50:50 (v/v) (A); DMSO/H_2O, 60:40 (v/v) (B); acetone/DMSO, 50:50 (v/v) (C); acetone/DMSO/H_2O/Tween 80, 15:35:15:35 (v/v) (D). The samples were tested between 6.4 and 19.6 kg/ha, due to the different molecular weights of the assayed compounds; in all the cases the employed amount of the product was 50 mol/ha. Five replications were done for each compound; a replication was represented by 40 seeds per cell. After treatment, the flats were placed in a greenhouse (20 °C), where they received regular watering (overhead). Evaluations were conducted until two to three true leaves were present after application (~2 weeks after treatment). Results of the greenhouse herbicide evaluation were expressed on a 0−4 rating scale (Eussen et al., 1990; Joshi et al., 1990; Karp et al., 1997). The scale is based on the determination of the decreasing of the following parameters: length of first leaf (lfl), aerial weight (aw), and radicular weight (rw) compared to those of an untreated control (with only carrier). In this scale, 1 represents minimum injury and 4 represents good activity (4 = 100 to 80% of reduction of the evaluated parameters with respect to the control, 3 = 79 to 50% of reduction of the evaluated parameters with respect to the control, 2 = 49 to 20% of reduction of the evaluated parameters with respect to the control, and 1 = 19 to 1% of reduction of the evaluated parameters with respect to the control); 0 represents increment of the parameters with respect to untreated control. Also, the percentage of germinated seeds was calculated. Atrazine was included in all of the assays to have a positive control (2.5 kg/ha, 12 mol/ha).

Post-emergence Herbicide Tests. Tests were prepared in an identical manner to the pre-emergence tests. After the weeds had three to four true leaves, the plants were treated with the test compound dissolved in carrier B. The spray chamber settings and application rates were identical to those of the pre-emergence treatments. After spraying, the plants were returned to the greenhouse and not watered overhead for 48 h. During these 2 days water was applied directly to the sand suface. The same evaluations were conducted 10 days after application.

Dose−Response Studies. This study was performed under conditions identical to those used for the pre-emergence herbicidal tests. The concentrations of compounds used were 12.0, 25.0, 50.0, and 75.0 mol/ha for derivatives **12** (2.400, 5.000, 10.000, and 15.000 kg/ha) and **20** (2.920, 6.150, 12.300, and 18.450 kg/ha). Because compound **26** showed the best herbicidal activity, we used lower concentrations, 0.1, 2.0 and 50.0 mol/ha (0.024, 0.472, and 11.800 kg/ha), in the dose−response studies.

Table 1. Pre-emergence Herbicidal Activity of *N*-Oxide Derivatives against *T. aestivum* L.

compd	dosage[a] (kg/ha)	carrier	activity[b,c] lfl	aw	rw	% of germinated seeds
1	9.5	B	1	0	1	100
2	13.1	B	2	0	2	100
3	13.1	C	2	0	3	100
4	10.5	B	1	1	1	100
5	16.9	B	I[d]	I	I	100
6	14.9	C	1	1	1	100
7	15.1	C	1	1	1	100
8	17.3	A	2	1	1	100
9	16.1	B	0	0	1	100
10	6.4	B	1	0	1	100
11	9.3	B		4	3	89
12	10.0	B	3	3	0	15
13	13.5	B	3	4	3	95
14	10.1	B		4	4	92
15	6.8	B	I	I	I	100
16	7.5	B	3	3	3	100
17	8.2	B	2	1	0	100
18	9.0	B	1	1	1	100
20	12.3	B	1	1	3	75
21	14.0	D	NS[e]	NS	NS	NS
22	16.3	B	2	2	2	100
23	15.0	D	NS	NS	NS	NS
24	11.9	B	2	1	1	100
25	12.5	B	3	3	3	100
26	11.8	B	3	3	3	46
27	14.5	B	3	3	4	96
28	14.5	D	0	0	0	100
29	19.0	D	0	0	1	100
30	16.0	B		4	3	75
31	17.7	D	2	0	4	90
32	19.6	D	3	4	4	84
33	18.1	B		3	3	90
34	11.0	B	0	0	0	100

[a] The employed amount of the product was 50 mol/ha. [b] Key to the parameters: length of first leaf (lfl), aerial weight (aw), radicular weight (rw). [c] Reduction of the parameter compared to an untreated control; 1 represents minimum injury, 4 represents maximum activity, and 0 represents increment of the parameters (see Biology under Materials and Methods). [d] I denotes that compound caused no injury to the target weed. [e] NS denotes that the results are not statistically significant, the solubility of the products is very low, and the biological activities are erratic.

Crystallography. Suitable needle-shaped single crystals of **9** were obtained by slow evaporation from EtOAc in the

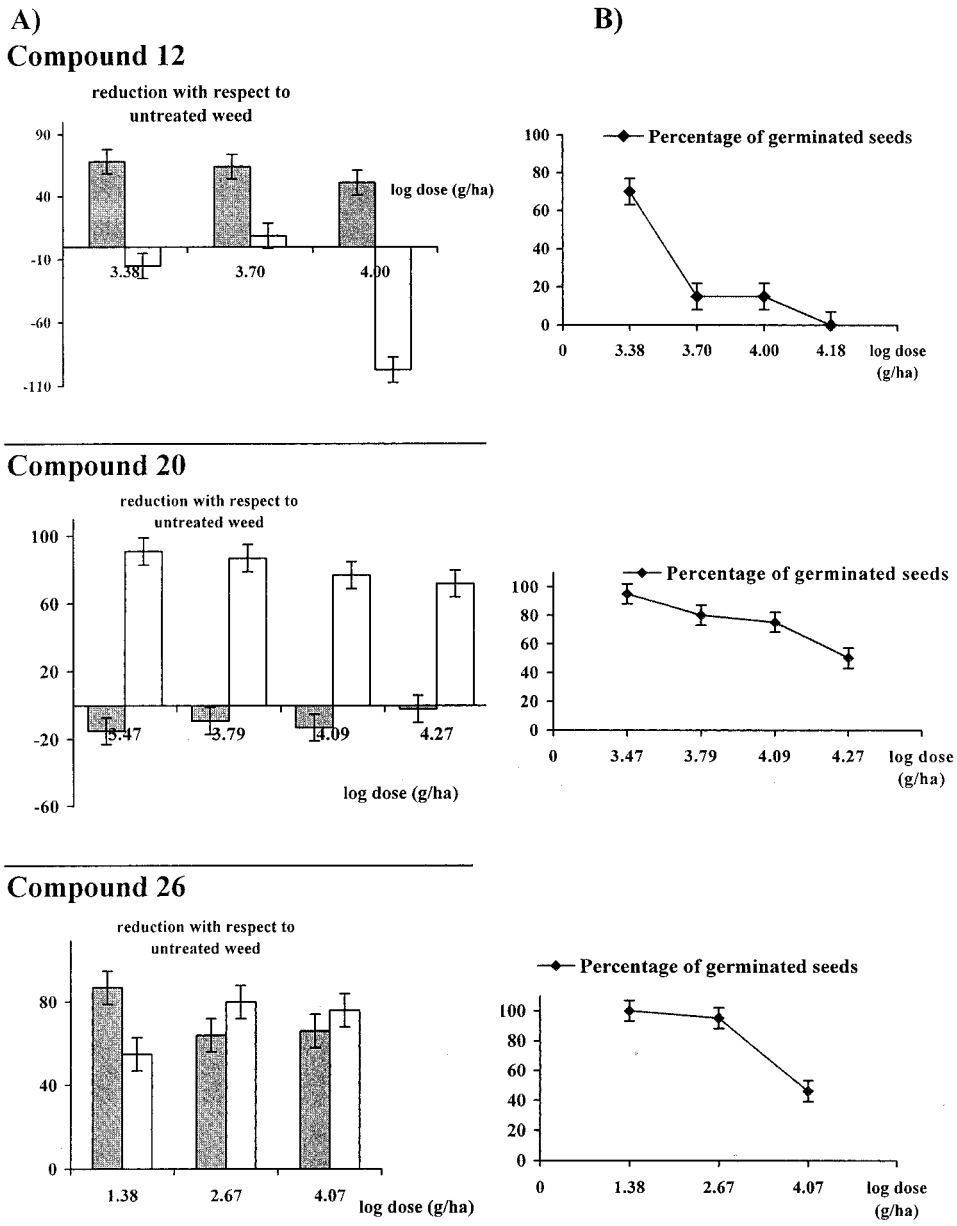


Figure 3. (A) Percentage of reduction of the evaluated parameters [aerial weight (shaded bars) and radicular weight (white bars)] with respect to the control at different doses for compounds **12**, **20**, and **26.** (B) Dose−response curves, log dose (g/ha) versus percentage of germinated seeds, for compounds **12**, **20**, and **26**.

monoclinic system. Space group is $P2_1/n$, with four molecules per unit cell, and cell constants of $a = 5.197(2)$ Å, $b = 18.883(3)$ Å, $c = 15.1147(17)$ Å, $\beta = 97.308(19)^o$, $V = 1471.1(6)$ Å^3. Intensities were collected in a Rigaku AFC7S diffractometer at room temperature with monocromated Mo Kα radiation ($\lambda = 0.7107$ Å). Of the 3333 collected reflections (range = 2.16° < θ < 27.48°), 2970 were independent and 1510 were observed ($I > 2\sigma I$). Structure was solved by direct methods, and all atoms were freely refined. Some conformational restraints were applied to the disordered phenyl ring to avoid unrealistic parameters (Sheldrick, 1990). The final residuals were $R_1 = 0.0788$ and $wR_2 = 0.2363$ for the observed reflections. Solutions and refinement of the structure were performed with the SHELX 97 package (Sheldrick, 1997).

RESULTS AND DISCUSSION

Synthesis. Our general strategy for the design of the structures was based on the conjunction of *N*-oxide systems and different functionalities (aldehyde, acid, semicarbazone, amine, and nitrile), to determine the optimum requirement for herbicidal activity.

The 1,2,5-oxadiazole derivatives were obtained as shown in Scheme 1. The benzo[1,2-*c*]1,2,5-oxadiazole system was prepared using the appropriate nitrophenyl azides (Scheme 2). Cyclocondensation of these azides in boiling toluene yielded the desired heterocycles. The semicarbazones **19**−**23** were obtained in variable yields (30−73%). The amides **24**−**27** were obtained in moderate yields.

The compounds **18**−**27** exist as a mixture of isomers at room temperature (**XV** and **XV′**, Figure 1). This phenomenon was observed through the corresponding NMR spectra (proton and carbon), which showed complex groups of signals in the aromatic zone (7.30−8.50 and 110−155 ppm, respectively) at room temperature. The spectra simplified at higher temperature, where one of these isomers predominates. Careful examination of coupling constants and chemical shifts indicated that the major isomer at high temperature is **XV**, which is the 1,5-disubstituted heterocycle (Harris et al., 1963; Boulton et al., 1967; Boulton and Middleton, 1974;

Cerecetto et al., 1999). On the other hand, compounds **1**−**14** were obtained as a single product (^{13}C NMR and crystallographic studies), and the *N*-oxide location was established by X-ray diffraction analysis. In this regard, the single-crystal X-ray structure of compound **9**, depicted in Figure 2, was used to confirm that the *N*-oxide moiety was not isomerized under the reaction conditions (Gasco et al., 1972; Calvino et al., 1993; Monge et al., 1998a).

In another effort to obtain new *N*-oxide derivatives, we expanded the oxadiazole system to obtain the quinoxaline 1,4-dioxide nucleus (Scheme 3). When compound **20** or **23** reacted with butanone in morpholine (Edwards and Bambury, 1975), the desired dimethylquinoxaline was not obtained. In both cases a main product was generated (intermediate **X**, characterized by ^1H NMR and MS), which could not be transformed into the desired product by treatment with Et_3N/MeOH at reflux. Therefore, we employed an alternative route to obtain the desired heterocycles, in which the aldehyde **XIII** was the carbonylic reactant. Beirut reaction of benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide with malononitrile in the presence of Et_3N at low temperature gave compounds **30**−**33** in good yields (73−80%) as a mixture of 6- and 7-substituted isomers (Ley and Seng, 1975; Albin and Pietra, 1991; Cheeseman and Cookson, 1979; Tennant and Mason, 1971).

The deoxygenated derivative **34** was prepared by reaction of the corresponding *N*-oxide (**20**) with Ph_3P in boiling EtOH (Scheme 3) (Howard and Olszewski, 1959).

Herbicidal Activity. The comparative herbicidal activity of the target compounds was measured at the whole plant level via a greenhouse assay (Table 1). Some of the *N*-oxide derivatives investigated showed activity in the pre-emergence tests. Compounds **21** and **23** were insoluble in all of the vehicles assayed; this fact yields to results that are not statistically significant (in some replications moderate activities were observed). The compounds evaluated in postemergence assays (**4**, **5**, **15**, and **18**) were not phytotoxic. Dose−response studies were performed for some of the more active compounds (**12**, **20**, and **26**) (Figure 3).

Herbicidal activity was very sensitive to the type of *N*-oxide supporting heterocycle. 4-Phenyloxadiazole *N*-oxide derivatives (compounds **1**−**9**) possess moderate to low pre-emergence activity. Compounds containing mesomeric electron-withdrawing groups at position 3 (e.g., compounds **2** and **3**) showed some level of activity. On the other hand, compounds containing inductive electron-withdrawing groups in this position (compounds **4**−**8**) were less active or inactive. 3-Methyloxadiazole *N*-oxide derivatives (**10**−**14**) were more active than the 4-phenyl analogues (comparing compounds with the same side chain, **12** to **2** and **14** to **3**). This family of compounds had high pre-emergence activity. The change of the phenyl group to the methyl in the 1,2,5-oxadiazole system could be playing an important role in the biological activity. Obviously, the different electronic effects of these moieties could be responsible for their dissimilar activities, but the lipophilic−hydrophilic contribution of these groups may also be important, affecting their transport through membranes. In general, the benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide derivatives (compounds **15**−**27**) were found to possess good pre-emergence activity. Herbicidal activity was sensitive to substitution at the *benzo* position (compare compound **15** with other derivatives, **16**−**18**, **20**, **22**, **24**−**27**). When the substituent was an amide, highest activities were found (**24**−**27**). The effect of amide-*N* substitution on herbicidal activity shows that lipophilicity may be also responsible for increased activity, and thus, compounds **26** and **27** were more active than compounds **24** and **25**. The expansion of the heterocycle to 2,3-dimethylquinoxaline di-*N*-oxides decreases activity (compare **28** to **20** and **29** to **22**). However, when the expansion was to 2-amino-3-cyanoquinoxaline di-*N*-oxides, the activity increased significantly (compare **30** to **20** and **32** to **22**). Finally, the absence of the *N*-oxide moiety produced a sharp loss of activity (see compounds **20** and **34**). Dose−response studies indicated that compounds **12** and **20** were active, even at a concentration 4 times lower than the initial (10.000 and 12.300 kg/ha, respectively). In addition, compound **26** was still active at a concentration 500 times lower than the initial concentration (11.800 kg/ha).

Studies determining cytotoxicity to mammalian cells for these groups of compounds showed that they have low toxicity (Monge et al., 1995, 1998a; Cerecetto et al., 1999).

In summary, a series of 1,2,5-oxadiazole *N*-oxide, benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide, and quinoxaline di-*N*-oxide derivatives were synthesized and evaluated for their herbicidal activities. Preliminary biological studies found that some of them exhibit significant herbicidal activity. The structural requirements indicated that the *N*-oxide moiety could be the phytophore, and electronic effects and the lipophilic−hydrophilic balance of the compounds may explain some differences in biological activity. Further studies, such as electrochemical measurements and EPR spectroscopy to determine the ability to form radicals, lipophilicity studies, and theoretical calculations, are currently in progress to determine mechanisms of action for these compounds.

LITERATURE CITED

Albin, A.; Pietra, S. *Heterocycles N-oxides*; CRC Press: Boca Raton, FL, 1991.

Baker, N. R.; Percival, M. P. Herbicides and photosynthesis. In *Herbicides. Topics in Photosynthesis*; Baker, N. R., Percival, M. P., Eds.; Barber, J., General Ed.; Elsevier Science Publishers: Amsterdam, The Netherlands, 1990; Vol. 10, Chapter 9.4, pp 1−26.

Boulton, A. J.; Middleton, D. Furazans and Furazan oxides. V. Tropono[4,5-*c*]-, Thieno[2,3-*c*]-, and Biphenyleno[2,3-*c*]-furazan oxides. *J. Org. Chem.* **1974**, *39*, 2956−2962.

Boulton, A. J.; Katritzky, A. R.; Sewell, M. J.; Wallis, B. *N*-Oxides and related compounds. XXXI. The nuclear magnetic resonance spectra and tautomerism of some substituted benzofuroxans. *J. Chem. Soc. B* **1967**, *9*, 914−917.

Boyer, J. H.; Ellzey, S. E. Deoxygenation of aromatic *o*-Dinitroso derivatives by phosphines. *J. Org. Chem.* **1961**, *26*, 4684−4685.

Cahill, A.; White, I. N. Reductive activation of *N*-oxides to cause DNA strand breakage in cell lines *in vitro. Biochem. Soc. Trans.* **1991**, *19* (2), 1275.

Calvino, R.; Di Stilo, A.; Fruttero, R.; Gasco, A. M.; Sorba, G.; Gasco, A. Pharmacochemistry of the furoxan ring: recent developments. *Farmaco* **1993**, *48* (2), 321−334.

Cerecetto, H.; Di Maio, R.; Ibarruri, G.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Paulino, M. Synthesis and antitrypanosomal activity of novel 5-Nitro-2-furaldehyde and 5-Nitrothiophene-2-carboxaldehyde semicarbazone derivatives. *Farmaco* **1998**, *53* (2), 89−94.

Cerecetto, H.; Di Maio, R.; González, M.; Risso, M.; Saenz, P.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Zinola, F.; Olea-Azar, C. 1,2,5-Oxadiazole *N*-oxide derivatives and

related compounds as potential antitrypanosomal drugs. Structure−activity relationship. *J. Med. Chem.* **1999**, *42*, 1941−1950.

Cheeseman, G. W. H.; Cookson, R. F. *Condensed Pyrazines*; Wiley: New York, 1979.

Clark, R. D. Synthesis and QSAR of herbicidal 3-pyrazolyl α,α,α-trifluorotolyl ethers. *J. Agric. Food Chem.* **1996**, *44*, 3643−3652.

Edwards, M. L.; Bambury, R. E. 2,3-Dimethylquinoxaline-6-carboxaldehyde 1,4-dioxide. *J. Heterocycl. Chem.* **1975**, *12* (5), 835−836.

Eussen, J. H. H.; Thus, J. L. G.; Wellinga, K.; Stork, B. 2-Pyrazolines with herbicidal activity. *Pestic. Sci.* **1990**, *29*, 101−108.

Fruttero, R.; Ferrarotti, B.; Serafino, A.; Di Stilo, A.; Gasco, A. Unsymmetrically substituted furoxans. Part 11[1]. Methylfuroxancarbaldehydes. *J. Heterocycl. Chem.* **1989**, *26*, 1345−1347.

Gasco, A.; Mortarini, V.; Ruà, G.; Nano, G. M.; Menziani, E. Synthesis and structure of some asymmetrically substituted furoxans. I. *J. Heterocycl. Chem.* **1972**, *9*, 577−580.

Gasco, A. M.; Fruttero, R.; Sorba, G.; Gasco A. Phenylfuroxancarbaldehydes and related compounds. *Justus Liebigs Ann. Chem.* **1991**, 1211−1213.

Harris, R. K.; Katritzky, A. R.; Oksne, S.; Bailey, A. S.; Paterson, W. G. *N*-Oxides and related compounds. Part XIX. Proton resonance spectra and the structure of benzofuroxan and its nitro-derivatives. *J. Chem. Soc.* **1963**, 197−203.

Hay, J. V. Chemistry of sulfonylurea herbicides. *Pestic. Sci.* **1990**, *29*, 247−261.

Howard, E.; Olszewski, W. F. The reaction of triphenylphosphine with some aromatic amine oxides. *J. Am. Chem. Soc.* **1959**, *81*, 1483−14847.

Joshi, K. C.; Jain, R.; Dandia, A.; Sharma, K.; Jain, S. C. Synthesis and pesticidal activities of certain fluorine-containing 9*H*-1,2,4-Triazolo[4,3-*a*]benzimidazoles. *Pestic. Sci.* **1990**, *29*, 143−149.

Karp, G. M.; Manfredi, M. C.; Guaciaro, M. A.; Ortlip, C. L.; Marc, P.; Szamosi, I. Synthesis and herbicidal activity of 1*H*-1,4-benzodiazepine-2,5-diones. *J. Agric. Food Chem.* **1997**, *45*, 493−500.

Kleschick, W. A.; Costales, M. J.; Dunbar, J. E.; Meikle, R. W.; Monte, W. T.; Pearson, N. R.; Snider, S. W.; Vinogradoff, A. P. New herbicidal derivatives of 1,2,4-triazolo[1,5-*a*]-pyrimidine. *Pestic. Sci.* **1990**, *29*, 341−355.

Ley, K.; Seng, F. Synthesis using benzofuroxanes. *Synthesis* **1975**, 415−422.

Monge, A.; López de Ceráin, A.; Ezpeleta, O.; Cerecetto, H.; Dias, E.; Di Maio, R.; González, M.; Onetto, S.; Seoane, G.; Suescun, L.; Mariezcurrena, R. Synthesis and biological evaluation of 1,2,5-oxadiazole *N*-oxide derivatives as hypoxia-selective cytotoxins. *Pharmazie* **1998a**, *53*, 758−764.

Monge, A.; López de Ceráin, A.; Ezpeleta, O.; Cerecetto, H.; Dias, E.; Di Maio, R.; González, M.; Onetto, S.; Risso, M.; Seoane, G.; Zinola, F.; Olea-Azar C. 1,2,5-Oxadiazole *N*-oxide derivatives as hypoxia-selective cytotoxins. Structure−activity relationships. *Pharmazie* **1998b**, *53*, 698−702.

Monge, A.; Palop, J. A.; López de Ceráin, A.; Senador, V.; Martínez-Crespo, F. J.; Sáinz, Y.; Narro, S.; García, E.; de Miguel, C.; González, M.; Hamilton, E.; Barker, A. J.; Clarke, E. D.; Greenhow, D. T. Hypoxia-selective agents derived from quinoxaline 1,4-di-*N*-oxides. *J. Med. Chem.* **1995**, *38*, 1786−1792.

Nandihalli, U. B.; Duke, M. V.; Ashmore, J. A.; Musco, V. A.; Clark, R. D.; Duke, O. S. Enantioselectivity of protoporphyrinogen oxidase-inhibiting herbicides. *Pestic. Sci.* **1994**, *40*, 265−277.

Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, U.K., 1988.

Sheldrick, G. M. Phase annealing in SHELX-90: direct methods for larger structures. *Acta Crystallogr.* **1990**, *A46*, 467−473.

Sheldrick, G. M. SHELXL-97, Program for structure refinement. University of Göttingen, Germany, 1997.

Smith, P. A. S.; Boyer, J. H. *Organic Syntheses Collective*; Rabjohn, N., Ed.; Wiley: New York, 1963; Vol. 4, pp 75−78.

Tennant, G.; Mason, J. C. Synthesis of 1-hidroxyquinoxalin-2(1H)-one 4-oxides. *J. Chem. Soc. D* **1971**, 586−587.

Theodoridis, G.; Hotzman, F. W.; Scherer, L. W.; Smith, B. A.; Tymonko, J. M.; Wyle, M. J. Synthesis and structure−activity relationships of 1-aryl-4-substituted-1,4-dihydro-5-*H*-tetrazol-5-ones, a novel class of pre- and post-emergence herbicides. *Pestic. Sci.* **1990**, *30*, 259−274.

Wepplo, P. Imidazolinone herbicides: synthesis and novel chemistry. *Pestic. Sci.* **1990**, *39*, 293−315.

Zsolnai, L.; Pritzkow, H. ZORTEP, An interactive ORTEP program. University of Heidelbelg, Germany, 1995.

Received for review May 7, 1999. Revised manuscript received February 28, 2000. Accepted April 26, 2000. This work was supported by CONICYT-Uruguay (Grant 347/95).

JF9904766