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Synthesis and Herbicidal Activity of the Halo Analogues of Pyoluteorin

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The synthesis of some halo analogues of pyoluteorin [2,3-dichloro-5-(2′,6′-dihydroxybenzoyl)-1*H*-pyrrole] through the use of a Friedel–Crafts aroylation of pyrrole with 2,6-dimethoxybenzoyl chloride, followed by halogenation and demethylation with boron tribromide, is described. Stepwise bromination of the intermediate 2-(2′,6′-dimethoxybenzoyl)pyrrole yielded the di-, tri-, and tetrabromo derivatives. Similarly, chlorination gave the dichloro and the trichloro derivatives whereas iodination with even an excess of iodine gave only the monoiodo derivative. A comparison of the herbicidal activity using a cress seedling assay indicated that some of the halo analogues were 2–40 times as active as the parent compound, pyoluterin, with the tribromo analogue being the most active. This activity range appears to be comparable to that seen with some of the commercially used herbicides tested in this assay.

Since the discovery of the antibiotic pyoluteorin (1) isolated from a *Pseudomonas spp.* by Takeda (1958a,b, 1959), a number of syntheses have been described (Elix and Sargent, 1967; Bailey and Rees, 1970; Birchall et al.,

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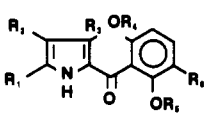
1970; Davies and Hodge, 1970; Durham et al., 1972; Bailey et al., 1973; Cue et al., 1981). We isolated 1 in a screening program and decided to prepare some of its other halo analogues and test them for their herbicidal activity based on a root growth inhibition type of assay. A modified synthetic approach was explored that was found to provide a more practical route to these compounds.

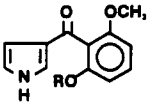
Friedel–Crafts aroylation of pyrrole with 2,6-dimethoxybenzoyl chloride in dichloroethane in the presence of aluminum chloride resulted in the formation of the desired 2-(2′,6′-dimethoxybenzoyl)-1*H*-pyrrole (2) (Cue et al., 1981) as the major product (70%) with a minor amount (8%) of the 3-isomer 3. The conditions used here appear to give greater overall yields (78%) compared to the 58% reported by the use of stannic chloride by Cue et al. (1981).

By the prior methods, compound 2 was demethylated first and then subjected to halogenation. However, it appeared that chlorination of 2 offered better control of the reaction with regard to the number of halogens introduced and their location. Thus, chlorination of 2 using *N*-chlorosuccinimide in carbon tetrachloride or chlorine in acetic acid gave mixtures of the dichloro and trichloro derivatives, readily separable by chromatography. Although the extent of chlorination and the product ratio depended on the amount of reagent used, use of an excess did not lead to the formation of the tetrachloro derivative, causing instead, degradation of the product. In contrast, addition of bromine in acetic acid to 2 in a stepwise fashion and stopping the reaction at the appropriate times gave the dibromo (6), the tribromo (7), and the tetrabromo derivative (8), relatively exclusively. In the case of iodination, only the monoiodo derivative (9) was formed regardless of the amount of reagent used.

After the halogenation step, the derivatives were all demethylated with boron tribromide in dichloromethane at −70 °C. As was noted by Birch et al. (1964), use of common demethylating agents produced an apparent reversal of the Friedal–Crafts aroylation. By the proper selection of the conditions, it was also possible to prepare the partially demethylated compounds.

Structures 1–18 represent the starting material and the various halogenated compounds and their partial and complete demethylation products. Tables I and II give the





1: $R_1 = R_2 = Cl$, $R_3 = R_4 = R_5 = R_6 = H$
2: $R_1 = R_2 = R_3 = R_6 = H$, $R_4 = R_5 = CH_3$
3: $R = CH_3$
4: $R_1 = R_2 = Cl$, $R_3 = R_6 = H$, $R_4 = R_5 = CH_3$
5: $R_1 = R_2 = R_6 = Cl$, $R_3 = H$, $R_4 = R_5 = CH_3$
6: $R_1 = R_2 = Br$, $R_3 = R_6 = H$, $R_4 = R_5 = CH_3$
7: $R_1 = R_2 = R_6 = Br$, $R_3 = H$, $R_4 = R_5 = CH_3$
8: $R_1 = R_2 = R_3 = R_6 = Br$, $R_4 = R_5 = CH_3$
9: $R_2 = I$, $R_1 = R_3 = R_6 = H$, $R_4 = R_5 = CH_3$
10: $R_1 = R_2 = Cl$, $R_3 = R_6 = R_4 = H$, $R_5 = CH_3$
11: $R_1 = R_2 = R_6 = Cl$, $R_3 = R_4 = R_5 = H$
12: $R_1 = R_2 = Br$, $R_3 = R_6 = R_4 = R_5 = H$
13: $R_1 = R_2 = R_6 = Br$, $R_3 = R_4 = R_5 = H$
14: $R_1 = R_2 = R_3 = R_6 = Br$, $R_4 = H$, $R_5 = CH_3$
15: $R_1 = R_2 = R_3 = R_6 = Br$, $R_4 = R_5 = H$
16: $R_2 = I$, $R_1 = R_3 = R_4 = R_5 = R_6 = H$
17: $R_1 = R_2 = R_3 = R_5 = R_6 = H$, $R_4 = CH_3$
18: R = H

important ^1H NMR and mass spectral data. Mass spectral fragmentation appears to represent the characteristic α-cleavage shown by aromatic ketones and is shown

Table I. ^1H NMR Spectra of Pyoluteorin and Its Analogues

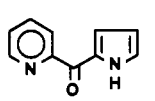
	pyrrole ring			phenyl ring			
carbon	C-3	C-4	C-5	C-3′	C-4′	C-5	NH/OH
1	6.42						9.46, 13.0
2	6.28	6.10	7.06	6.7	7.33	6.7	10.4
4	6.48			6.66	7.36	6.66	9.8
5	6.55				7.52	6.94	13.3
6	6.39			6.73	7.38	6.73	9.8
7	6.58				7.66	6.90	9.8
8					7.66	6.38	13.6
9	6.41		7.25	6.75	7.40	6.75	12.2
10	6.55			6.60	7.32	6.80	9.8
11	6.55				7.48	7.28	9.45–9.85, 13.3
12	6.46			6.41	7.10	6.41	9.5, 13.1
13	6.53				7.40	6.45	9.28–9.85, 13.2
14					7.60	6.68	9.5, 13.4
15					7.38	6.4	9.3–9.9, 13.4
16	6.45		7.22		7.05	6.38	9.4, 12.0

Table II. Mass Spectral Data on Pyoluterin and Analogues

compd	M·+, %	pyrrole frag,[a] %	phenyl frag,[b] %
1	271 (30)	135 (30)	137 (100)
2	231 (100)	66 (36)	165 (35)
4	299 (55)	135 (15)	165 (85)
5	335 (90)	134 (30)	199 (70)
6	389 (35)	224 (8)	165 (48)
7	467 (100)	224 (35)	245 (38)
8	546 (100)	303 (16)	245 (60)
9	357 (65)	193 (5)	165 (28)
10	285 (5)	135 (5)	151 (96), 150 (100)
11	305 (22)	135 (65)	171 (80), 170 (100)
12	359 (30)	275 (35)	137 (100), 136 (58)
13	439 (20)	225 (38)	216 (40)
14	533 (5)	303 (12)	230 (10)
15	519 (15)	303 (15)	216 (55)
16	329 (82)	193 (84)	136 (100)

in Table II, with the pyrrole fragment being designated as a and the benzenoid fragment designated as b.

In an extension of the above procedures, picolinoyl and nicotinoyl chlorides were also condensed with pyrrole in the presence of aluminum chloride to yield ketones 19 and 20. Chlorination of 19 readily gave trichloro deriv-



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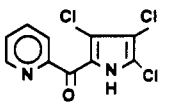

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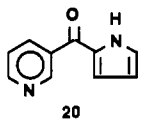

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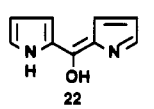

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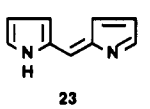

23

ative 21. Reaction of 1*H*-pyrrole-2-carboxylic acid chloride with pyrrole, on the other hand, produced a dark bluish compound that showed its major UV maximum at 335 nm and no carbonyl absorption in its IR spectrum. On the basis of these and ^1H NMR and mass spectral data, the compound was assigned structure 22. This structure is analogous to the dipyrrolylmethene structure proposed for product 23 obtained from pyrrole-2-carboxaldehyde and pyrrole in the presence of hydrogen bromide (Acheson, 1960).

EXPERIMENTAL SECTION

General Procedures. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. The follow-

ing conditions and instrumentation were used for obtaining the spectra described: UV, EtOH, Perkin-Elmer Lambda 3B; IR, KBr pellet, Beckman Acculab 3; NMR, $CDCl_3$, unless otherwise specified, with TMS as internal standard, Varian EM 390 and MS, Kratos MS80RFA. Chemical shifts are given in ppm, and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was carried out with silica gel (Merck, <0.063 mm), and TLC, on silica gel (Merck, H60, P254/366).

2-(2′,6′-Dimethoxybenzoyl)-1*H*-pyrrole (2) and 3-(2′,6′-Dimethoxybenzoyl)-1*H*-pyrrole (3). To a mixture of pyrrole (1 mL) and 2,6-dimethoxybenzoyl chloride (2 g) in dichloroethane (20 mL) cooled to 5 °C was added a slurry of anhydrous aluminum chloride (1.5 g) in dichloromethane (20 mL) while stirring over a period of 30 min. After the mixture was stirred for 1 h at 20 °C, water was added to decompose the acid chloride and the organic layer washed with water, dried, and concentrated to dryness. The residue was taken up in benzene (20 mL) and subjected to chromatography on silica gel. Elution with 2% acetone in benzene gave the major component **2**: yield 1.4 g; mp 189–91 °C [lit. (Cue et al., 1981) mp 191–193 °C]; UV λ_{max} 295 nm. Further elution with 5% acetone in benzene gave **3**: yield 0.12 g; mp 198–200 °C [lit (Cue et al., 1981) mp 200–202 °C]; UV λ_{max} 248, 272 (sh) nm.

Chlorination of 2 To Form 4 and 5. To a cooled (5%) solution of **2** (0.46 g) in chloroform (20 mL) was added *N*-chlorosuccinimide (0.38 g) and the mixture stirred at 5 °C for 1 h and then at 25 °C for 2 h. After the mixture was washed with aqueous sodium bisulfite followed by water and dried, the solvent layer was concentrated to dryness and the product subjected to preparative TLC in 10% ethyl acetate in benzene. The band with the higher R_f gave 3′-chloropyoluteorin dimethyl ether (**5**) crystallized from benzene–hexane: yield 0.15 g; mp 172–174 °C [lit. (Durham et al., 1972) mp 174–176 °C]. The slower moving band gave after crystallization from benzene–hexane **4**: yield 0.14 g; mp 185–188 °C.

Bromination of 2. Bromine (0.15 mL) in acetic acid (5 mL) was added to a solution of **2** (0.6 g) in acetic acid (10 mL) at 20 °C and the mixture stirred for 1 h. After removal of the excess bromine with aqueous sodium bisulfite followed by washing with water and drying, the chloroform layer was concentrated and the solid crystallized from benzene to yield **6**: 0.4 g; mp 204–206 °C [lit. (Bailey et al., 1973) mp 200–205 °C].

When the reaction was carried out with 3 mol equiv of bromine, the main product, obtained by crystallization from benzene–hexane, was **7**: yield 0.45 g; mp 183–185 °C; UV λ_{max} 310 nm; IR 3220, 1620, 1580, 1460, 1375, 1280, 1090, 900, 790 cm^{-1}. Anal. Calcd for $C_{13}H_{10}NO_3Br_3$: C, 33.36; H, 2.15; N, 2.99; Br, 51.23. Found: C, 33.46; H, 2.16; N, 2.97; Br, 51.30.

With 5–6 mol equiv of bromine and a reaction time of 16 h, the product was crystallized from benzene–hexane to yield **8**: 0.6 g; mp 198–199 °C; UV λ_{max} 310 nm; IR 3200, 1630, 1590, 1375, 1290, 1090, 800 cm^{-1}. Anal. Calcd for $C_{13}H_9NO_3Br_4$: C, 28.55; H, 1.66; N, 2.56; Br, 58.45. Found: C, 28.75; H, 1.89; N, 2.28; Br, 58.11.

Iodination of 2 To Form 9. Compound **2** (0.12 g) in acetic acid (10 mL) was stirred while solid iodine (0.4 g) was added in portions over 1 h. After being stirred for 16 h, the mixture was diluted with water, decolorized with sodium bisulfite, and extracted twice with chloroform. The extract was washed with water, dried, and concentrated to dryness. After chromatography on silica gel, in chloroform, the major product **9** was obtained as colorless crystalline solid: yield 0.08 g; mp 164–165 °C; UV λ_{max} 258, 305 nm; IR 3340, 3280, 1630, 1590, 1370, 1250, 1100, 900, 750, 710 cm^{-1}. Anal. Calcd for $C_{13}H_{12}NO_3I$: C, 43.72; H, 3.39; N, 3.92; I, 35.54. Found: C, 43.64; H, 3.36; N, 3.92; I, 35.56.

General Procedure for Demethylations. The sample (1 mM) in dichloromethane (10–20 mL) was cooled to −70 °C, treated with boron tribromide (2.2 mM) in dichloromethane (10 mL), stirred at −70 °C for 2–4 h, and then left for 16–20 h at room temperature. The excess reagent was decomposed by cautious addition of water (20 mL). The organic layer was separated, washed with water, dried, and concentrated to dryness. The product was directly crystallized.

By this procedure **5** (0.1 g) gave **11** (0.65 mg), mp 204–206 °C [lit. (Durham et al., 1972) mp 200–205 °C].

Compound **2** (0.5 g) yielded **17** (0.3 g): mp 117–118 °C; UV λ_{max} 296 nm. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.19; H, 5.25; N, 6.22.

Compound **4** (0.1 g) formed **1** (0.03 g) [mp 182–184 °C [lit. (Bailey et al., 1973) mp 175–182 °C]] (identical with natural pyoluteorin) and **10** (0.04 g) [mp 115–118 °C]. Anal. Calcd for $C_{12}H_9NO_3Cl_2$: C, 50.37; H, 3.17; N, 4.89; Cl, 24.79. Found: C, 50.25; H, 3.29; N, 5.01; Cl, 24.98.

Compound **6** (0.12 g) produced **12** (0.065 g), mp 175–176 °C [Lit. (Bailey et al., 1973) mp 163–164 °C].

Compound **7** (0.1 g) yielded **13** (0.05 g): mp 180–182 °C; UV λ_{max} 310, 362 nm; IR 3480, 3410, 3200, 1605, 1580, 1440, 1390, 1205, 970, 830 cm^{-1}. Anal. Calcd for $C_{11}H_6NO_3Br_3$: C, 30.03; H, 1.37; N, 3.18; Br, 54.50. Found: C, 29.89; H, 1.55; N, 3.31; Br, 54.19.

Compound **8** (0.15 g) produced **14** (0.06 g): mp 176–177 °C; UV λ_{max} 293, 362 (sh) nm; IR 3200, 1610, 1575, 1520, 1455, 1220, 1125, 1090, 795 cm^{-1}. Anal. Calcd for $C_{12}H_7NO_3Br_4$: C, 27.05; H, 1.32; N, 2.63; Br, 60.00. Found: C, 27.21; H, 1.45; N, 2.51; Br, 59.69. **15** (0.03 g): mp 150 °C dec; UV λ_{max} 310, 360 (sh) nm; IR 3300, 1620, 1600, 1460, 1390, 1210, 920, 820 cm^{-1}. Anal. Calcd for $C_{11}H_5NO_3Br_4$: C, 25.46; H, 0.97; N, 2.70; Br, 61.61. Found: C, 25.30; H, 1.01; N, 2.67; Br, 61.37.

Compound **9** (0.2 g) formed **16** (0.12 g): mp 180–182 °C; UV λ_{max} 258, 306 nm; IR 3460, 3400, 3310, 1630, 1590, 1370, 1190, 900, 780 cm^{-1}. Anal. Calcd for $C_{11}H_8NO_3I$: C, 40.24; H, 2.45; N, 4.26; I, 38.66. Found: C, 40.29; H, 2.49; N, 4.27; I, 38.51.

2-Picolinoyl-1*H*-pyrrole 19. To a solution of picolinoyl chloride (1.32 g) in dichloroethane, cooled to 0–5 °C, were added aluminum chloride (1 g) and then pyrrole (1 mL). After 2 h, the reaction mixture was diluted with ice water and the organic layer separated. It was washed with water, dried, and concentrated to dryness. The solid was crystallized from benzene–hexane: yield 1 g; mp 65–67 °C; UV λ_{max} 270, 326 nm; IR 3350, 1620, 1580, 1405, 1060, 780 cm^{-1}; NMR δ 6.35 (m, H-4), 7.1 (m, H-3), 7.48 (m, H-5), 7.5 (m, H-4′), 7.9 (dt, J = 8, 1.5 Hz, H-5′), 8.28 (d, J = 8 Hz, H-3′), 8.68 (d, J = 8 Hz; H-6′); MS 172 ($M^{\bullet+}$, 22), 145 (20), 117 (25), 85 (92), and 57 (100)). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.69; H, 4.73; N, 16.26.

2-Picolinoyl-3,4,5-trichloro-1*H*-pyrrole (21). A solution of chlorine in acetic acid representing 4 equiv of chlorine/mol of **19** was added to a suspension of **19** (0.1 g) in acetic acid (3 mL). After 2 h, the mixture was diluted with water containing $NaHSO_3$ and extracted with chloroform. The extract was washed with aqueous $NaHCO_3$, dried, and concentrated to dryness. The product was crystallized from benzene: yield 0.12 g; mp 170–172 °C; UV λ_{max} 274, 332 nm; IR 3290, 3240, 1620, 1580, 1450, 840, 740 cm^{-1}; NMR (DMSO-d_6) δ 7.7 (m, H-3′), 8.05 (m, H-4′ and H-5′) and 8.8 (m, H-6′); MS 274 ($M^{\bullet+}$, 10), 240 (90), 212 (60), 206 (95), 178 (90), 162 (60), 128 (100), 79 (90). Anal. Calcd for $C_{10}H_5N_2OCl_3$: C, 43.59; H, 1.83; N, 10.17; Cl, 38.61. Found: C, 43.40; H, 1.96; N, 10.48; Cl, 38.28.

2-Nicotinoyl-1*H*-pyrrole (20). The procedure used for **19** was followed except that nicotinoyl chloride was used. The product was crystallized from benzene–hexane: yield 1 g; mp 127–128 °C; UV λ_{max} 310 nm; IR 3140, 3080, 1625, 1585, 1400, 890, 730 cm^{-1}; NMR δ 6.38 (m, H-4), 6.92 (m, H-3), 7.24 (m, H-5), 7.45 (dd, J = 8 Hz, H-5′), 8.2 (dt, J = 8, 1.5 Hz, H-4′), 8.8 (dd, J = 7, 1.5 Hz, H-6′), 9.15 (d, J = 1.5 Hz, H-2′); MS 172 ($M^{\bullet+}$, 95), 145 (55), 117 (32), 94 (100), 78 (82). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.89; H, 4.85; N, 16.34.

(1*H*-Pyrrol-2-yl)(2*H*-pyrrolylidene)methanol (22). The procedure used under **19** was used except that 1*H*-pyrrole-2-carboxylic acid chloride was used. The product was crystallized from benzene–hexane: yield 0.6 g; mp 150–152 °C; UV λ_{max} 258, 335 nm; IR 3430, 3380, 1590, 1570, 1405, 1100, 1035, 835, 750 cm^{-1}; NMR δ 6.34 (m, 1 H), 7.1 (m, 1 H), 7.18 (m, 1 H), 10.4 (m, 1 H, exchangeable); MS, 160 ($M^{\bullet+}$, 85), 94 (68), 67 (100). Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.28; H, 5.06; N, 17.40.

Root Growth Inhibition Assay. The compounds were tested for their root growth inhibitory activity by a modification of

Table III. Herbicidal Activity of Pyoluteorin and Its Halo Analogues and That of Some Commercial Herbicides

compd	ED_{50}, M	rel act.
1	2×10^{-5}	1
11	1.3×10^{-6}	15
12	3×10^{-6}	6.7
13	5×10^{-7}	40
15	4×10^{-6}	5
16	1.2×10^{-4}	0.17
10	$>10^{-3}$	
14	1×10^{-5}	2
Rodeo	1.4×10^{-4}	0.14
Treflan	3.5×10^{-5}	0.57
Diquat	2×10^{-5}	1
Chlorsulfuran	1.3×10^{-5}	1.5
Thiadiazuron	1×10^{-5}	2
Mariner	2×10^{-4}	0.1
2,4-D-amine	2.7×10^{-7}	74

the procedure described by Noel et al. (1979). In this test, cress seedlings (*Lepidium sativum*) were allowed to grow on agar, instead of the methylcellulose as described by Noel et al. (1979), containing the test compound. The compounds were all dissolved in dimethyl sulfoxide to make, for example, a 1% solution such that a 0.2-mL aliquot when diluted by the addition of 20 mL of agar gave a concentration of 100 ppm. Other dilutions were prepared accordingly. After 24 h, the length of the root was measured and compared with that of the control to obtain the percent inhibition readings. The samples were tested in triplicate, and the average values were used. The ED_{50} values were obtained from the linear relationship between the log concentration and the percent inhibition. Table III gives a comparison of the activities.

RESULTS AND DISCUSSION

The root growth inhibition assay used here is a very sensitive and reproducible method of measuring the activity of compounds that exert their effects after being absorbed by the roots. For purposes of comparison, a few commercially available herbicides are also included in the test. The following compounds are tested: (1) Rodeo (isopropylamine salt of glyphosate, Monsanto), (2) Mariner (methyl 2-[[[[[(4,6-dimethoxypyrimidin-2-yl)amino]carbonyl]amino]sulfonyl]methyl]benzoate, Du Pont), (3) Thiadiazuron (*N*-phenyl-*N*-thiadiazid-5-ylurea, Noram), (4) Treflan (2,6-dinitro-*N*,*N*-dipropyl-4-(trifluoromethyl)benzeneamine, Lilly), (5) Diquat dibromide (6,7-dihydropyrido[1,2-*a*:2′,1′-*c*]pyrazinediium dibromide, ICI), (6) 2,4-D-amine (an amine salt of 2,4-dichlorophenoxyacetic acid, Amchen), and (7) chlorosulfuron (2-chloro-*N*-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]benzenesulfonamide, Du Pont). Results on all these compounds are also shown in Table III.

Ohmuri et al. (1978) described the antibacterial activity of pyoluteorin against some plant pathogenic bacteria and herbicidal activity against some plant species grown under both wet and dry conditions, with the drug added pre- as well as postemergence. They found that **1** was active mostly when used under dry conditions and in the postemergence treatment. Of the four species tested, at the rate of 50 g/acre, crab grass was the most sensitive, the three others being moderately sensitive.

Pyoluteorin and its halo analogues show significant root growth inhibitory activity in the test described here. On a molar basis, the analogues appear to be 2–40 times more active than pyoluterin. The most active analogue is tribromo compound **13**, followed by trichloro derivative **11**. The monomethyl ethers appear to be less active than the corresponding dihydroxy compounds. Of the two examples tested, **10**, the monomethyl ether of **1**, was inactive at the levels tested and **14**, the monomethyl ether of **13**, was active at a much less extent than **13** but still more active than **1**. The pyridine analogues made from **19** and **20** were inactive.

Surprisingly, many of the commercial herbicide samples tested here showed only marginal activity in this test, or activity of the same order of magnitude as that of pyoluteorin. This may indicate that these are not readily absorbed by the roots. However, they must all be absorbed by the leaves since all are used effectively as sprays on the leaf. Of the seven tested here, Diquat appears to be as active as pyoluteorin, with Thiadiazuron being twice as active and Treflan half as active as **1**. The most active agent tested here is 2,4-D-amine, which appears to be nearly 75 times as active as **1**.

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