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DIHYDROPHENANTHRENE AND PHENANTHRENE MIMICS OF NATURAL COMPOUNDS—SYNTHESIS AND ANTIALGAL ACTIVITY

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Abstract—9,10-Dihydrophenanthrenes and phenanthrenes, mimics of natural compounds with strong antialgal activity, have been synthesized through cross-coupling of 1-(2-iodo-5-methoxy)-phenylethanol with variously substituted iodobenzenes. The synthetic compounds, bearing a hydroxyl or a methoxyl group at C-2 and a methyl in the C ring, were tested against the green alga *Selenastrum capricornutum*. All compounds, except 2-methoxy-7-methylphenanthrene, caused inhibition of algal growth by more than 70% at 10^{-4} M, and many of them retained this strong activity at 10^{-5} M.

Key Words—*Juncus effusus*, phenanthrenes, 9,10-dihydrophenanthrenes, cross-coupling, algicides, *Selenastrum capricornutum*.

INTRODUCTION

Algal bloom is symptomatic of the later stages of eutrophication of waterbodies, and although the reduction of nutrients remains the most effective method for the control of the algal growth, in many cases, as in the waters receiving sewage effluents or nutrients from agriculture, the use of algicides becomes a necessity.

There is a conflict between the need for powerful algicides and the requirement of safe and harmless compounds (Milne and Callow, 1985). None of the

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six active ingredients (Anderson and Dechoretz, 1984) currently used for algal control in waters for fishing, aquaculture, irrigation, and swimming can be utilized in large-scale treatments in natural environments owing to their harmful effects on aquatic fauna.

In connection with a study of the allelopathic interactions of macrophytes and microalgae (DellaGreca et al., 1995a), we have isolated from the wetland plant *Juncus effusus* 25 free and 9 glucosylated 9,10-dihydrophenanthrenes (DellaGreca et al., 1992, 1993, 1995b,c, 1997). From the same species, some corresponding phenanthrenes have also been isolated (Shima et al., 1991). Many of the free compounds are strongly active against the green alga *Selenastrum capricornutum* (DellaGreca et al., 1996), one of the organisms recommended for the standard algal assay procedure developed for aquatic systems (Pipe and Shubert, 1984). Some of these compounds, in contrast, are inactive at the same concentrations against the brine shrimp *Artemia salina*. On this basis, we planned a synthesis of 9,10-dihydrophenanthrenes and phenanthrenes, mimics of the natural compounds, with a hydroxyl or a methoxyl group at the C-2 position of the A ring and a methyl in the C ring, to test them as algicides.

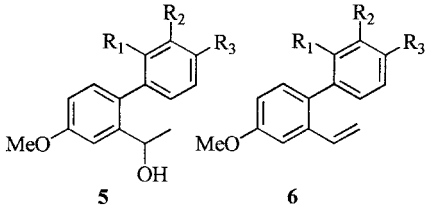
The synthesis was based on the cross-coupling of 1-(2-iodo-5-methoxy)-phenylethanol with various substituted iodobenzenes by zerovalent nickel (Semmelhack et al., 1981).

METHODS AND MATERIALS

Chemicals. 3-Hydroxyacetophenone and iodobenzenes were obtained commercially (Aldrich).

General Experimental Procedures. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a Bruker AC 400 spectrometer in $CDCl_3$ solutions. One-bond and long-range H—C COSY experiments were performed with the XHCORR microprogram by using delays corresponding to $J_{C,H}$ = 160 Hz and 8 Hz, respectively. HPLC was performed on a Varian Vista 5500 by using an UV detector.

*Synthesis of 1-(2-iodo-5-methoxy)-phenylethanol (**1**).* To a solution of 3-hydroxyacetophenone (**2**) (2.7 g; 20 mmol) in EtOH (6 ml) and 2 N NaOH (10 ml), Me_2SO_4 (5 ml) was added after 10 min, and the reaction mixture was kept at room temperature for 4 hr. Acidification by 2 N H_2SO_4 and extraction with Et_2O gave 3-methoxyacetophenone (**3**) (3.0 g), which, dissolved in MeOH (10 ml), was directly reduced by $NaBH_4$ excess. After 1 hr, AcOH was added, and the mixture was extracted with Et_2O to give 1-(3-methoxy)-phenylethanol (**4**) quantitatively. That compound (3.0 g; 20 mmol), dissolved in CH_2Cl_2 (20 ml), was treated with I_2 (5.1 g; 20 mmol) and CF_3COOAg (4.5 g; 20 mmol). After 2 hr, aq 10% $NaHSO_3$ was added, and extraction with CH_2Cl_2 gave a crude product that was chromatographed on silica gel (hexane–Et_2O 4 : 1) to afford

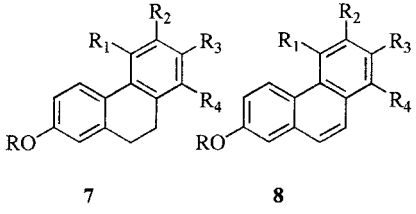


	R_1	R_2	R_3
a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me

FIG. 1. Intermediates in the synthesis.

pure **1** (4.97 g; 18 mmol; 90%): ^{1}H NMR δ 7.66 (1H, d, J = 8.4 Hz, H-3), 6.59 (1H, dd, J = 2.1 and 8.4 Hz, H-4), 7.18 (1H, d, J = 2.1 Hz, H-6), 5.03 (1H, q, J = 6.4 Hz, H-7), 1.46 (3H, d, J = 6.4 Hz, H-8), 3.82 (3H, s, OMe); ^{13}C NMR δ 148.6 (C-1), 85.3 (C-2), 139.7 (C-3), 115.4 (C-4), 160.4 (C-5), 112.0 (C-6), 73.6 (C-7), 23.7 (C-8), 55.4 (OMe).

*Synthesis of 2-Hydroxy-9,10-dihydrophenanthrene (**7b**) and 2-Hydroxyphenanthrene (**8b**) (Figures 1 and 2).* To a 50-ml three-necked flask, zinc dust (392 mg, 6 mmol washed with 2 N HCl, H_2O, EtOH, Me_2CO, and Et_2O and dried in oven at 120°C), $NiCl_2$ (784 mg, 6 mmol), PPh_3 (6.3 g, 24 mmol), and dry DMF (10 ml) were added. The mixture was warmed at 40°C under N_2 and stirred for 1 hr; a solution of **1** (834 mg, 3 mmol) and iodobenzene (612 mg, 3 mmol) in dry DMF (5 ml) was added at once, and the reaction mixture was kept at 40°C for 6 hr. 2 N NH_4OH was added, and the mixture was extracted with Et_2O. After evaporation, the residue was chromatographed on silica gel (benzene–Et_2O 19 : 1) to afford biphenyl **5a** (320 mg, 1.4 mmol, 47%): ^{1}H NMR δ 6.86 (1H, dd, J = 2.4 and 8.3 Hz, H-5), 7.16 (1H, d, J = 8.3 Hz, H-6), 7.22–7.44 (6H, m, H-3, H-2′–H-6′), 5.00 (1H, q, J = 6.4 Hz, H-7), 1.40 (3H, d, J = 6.4 Hz, H-8), 3.88 (3H, s, OMe); ^{13}C NMR δ 132.8 (C-1), 144.4 (C-2), 110.3 (C-3), 159.4 (C-4), 112.9 (C-5), 131.1 (C-6), 66.5 (C-7), 25.1 (C-8), 55.3 (OMe), 140.6 (C-1′), 128.1 (C-2′ and C-6′), 129.5 (C-3′ and C-5′), 126.6 (C-4′).



	R	R_1	R_2	R_3	R_4
a	Me	H	H	H	H
b	H	H	H	H	H
c	Me	Me	H	H	H
d	H	Me	H	H	H
e	Me	H	Me	H	H
f	H	H	Me	H	H
g	Me	H	H	Me	H
h	H	H	H	Me	H
i	Me	H	H	H	Me
l	H	H	H	H	Me

FIG. 2. Synthetic phenanthrenes and 9,10-dihydrophenanthrenes.

To a solution of **5a** (320 mg, 1.4 mmol) in dry xylene (1 ml), I_2 (20 mg, 0.08 mol) was added, and the mixture was kept at 140°C for 6 hr. Addition of 10% aq $NaHSO_3$ and extraction with Et_2O gave a residue that, chromatographed on silica gel (hexane), **6a** (252 mg, 1.2 mmol, 86%): ^{1}H NMR δ 6.93 (1H, dd, J = 2.3 and 8.3 Hz, H-5), 7.11–7.45 (7H, m, H-3, H-6, H-2′–H-6′), 6.74 (1H, dd, J = 10.8 and 17.5 Hz, H-7), 5.71 (1H, dd, J = 1.8 and 17.5 Hz, H-8), 5.22 (1H, dd, J = 1.8 and 10.8 Hz, H-8), 3.90 (3H, s, OMe); ^{13}C NMR δ 133.7 (C-1), 136.7 (C-2), 110.5 (C-3), 158.9 (C-4), 113.5 (C-5), 131.2 (C-6), 135.3 (C-7), 114.7 (C-8), 55.3 (OMe), 140.5 (C-1′), 127.9 (C-2′ and C-6′), 129.8 (C-3′ and C-5′), 126.6 (C-4′).

A sample of **6a** (120 mg, 0.57 mmol) in dry benzene (6.5 ml) under an argon atmosphere was irradiated with a 450-W Hanovia lamp at room temperature for 30 min under magnetic stirring. Chromatography on silica gel (hexane–benzene 19 : 1) gave **7a** (63 mg, 0.30 mmol) along with unreacted **6a** (52 mg). After purification by HPLC-NH_2 (hexane–isopropyl ether 99.8 : 0.2), **7a** had: ^{1}H NMR δ 6.84 (1H, d, J = 2.3 Hz, H-1), 6.88 (1H, dd, J = 2.3 and 8.4 Hz, H-3), 7.73 (1H, d, J = 8.4 Hz, H-4), 7.67 (1H, d, J = 8.1 Hz, H-5), 7.25 (3H, m, H-6, H-7 and H-8), 2.91 (2H, brs, H-9 and H-10); ^{13}C NMR δ 112.3 (C-1), 161.0 (C-2), 113.5 (C-3), 124.9 (C-4), 123.0 (C-5), 126.5 (C-6), 127.0 (C-7), 128.0 (C-8), 29.5 (C-9), 29.1 (C-10), 139.0 (C-1a), 127.5 (C-4a), 136.5 (C-5a), 134.5 (C-8a) 55.2 (OMe).

To a solution of **7a** (105 mg, 0.5 mmol) in dry CH_2Cl_2 (5 ml) cooled at −70°C, BBr_3 (350 μl) was added. Addition of 1 N $NaHCO_3$ after 3 hr and extraction with $CHCl_3$ gave a residue that was purified by preparative TLC (hexane–Et_2O 1 : 1) to give **7b** (69 mg, 0.35 mmol, 70%): ^{1}H NMR δ 6.73 (1H, d, J = 2.5 Hz, H-1), 6.79 (1H, dd, J = 2.5 and 8.3 Hz, H-3), 7.66 (1H, d, J = 8.3 Hz, H-4), 7.67 (1H, d, J = 8.1 Hz, H-5), 7.23 (3H, m, H-6, H-7, and H-8), 2.86 (4H, brs, H-9 and H-10); ^{13}C NMR δ 113.9 (C-1), 155.0 (C-2), 115.0 (C-3), 125.2 (C-4), 123.0 (C-5), 126.6 (C-6), 127.0 (C-7), 128.1 (C-8), 29.3 (C-9), 29.0 (C-10), 139.2 (C-1a), 127.9 (C-4a), 136.1 (C-5a), 134.2 (C-8a).

A sample of **6a** (120 mg, 0.57 mmol) in dry benzene (6.5 ml) was irradiated with a 450-W Hanova lamp for 25 min at room temperature under magnetic stirring in the presence of atmospheric oxygen. Chromatography on silica gel (hexane) afforded **8a** (64 mg, 0.31 mmol), unreacted **6a** (50 mg), and **7a** (3 mg). **8a** had: ^{1}H NMR δ 7.32 (1H, d, J = 1.6 Hz, H-1), 7.31 (1H, dd, J = 1.6 and 8.4 Hz, H-3), 8.62 (2H, d, J = 8.4 Hz, H-4 and H-5), 7.64 (1H, ddd, J = 1.4, 8.3, 8.4 Hz, H-6), 7.58 (1H, ddd, J = 1.4, 8.3 and 8.4 Hz, H-7), 7.91 (1H, dd, J = 1.4 and 8.3 Hz, H-8), 7.74 (2H, d, J = 9.6 Hz, H-9 and H-10), 3.99 (3H, s, OMe); ^{13}C NMR δ 117.1 (C-1), 158.3 (C-2), 108.7 (C-3), 124.3 (C-4), 122.2 (C-5), 126.5 (C-6), 126.7 (C-7), 128.6 (C-8), 127.6 (C-9), 125.6 (C-10), 133.5 (C-1a), 124.8 (C-4a), 130.4 (C-5a), 131.1 (C-8a), 55.4 (OMe).

BBr_3 (350 μl) treatment of **8a** (105 mg, 0.50 mmol) in dry CH_2Cl_2 (5 ml)

at −70°C for 3 hr gave **8b** (71 mg, 0.36 mmol): ^{1}H NMR δ 7.26 (1H, d, *J* = 1.5 Hz, H-1), 7.25 (1H, dd, *J* = 1.5 and 8.4 Hz, H-3), 8.58 (2H, d, *J* = 8.4 Hz, H-4 and H-5), 7.63 (1H, ddd, *J* = 1.4, 8.3, 8.4 Hz, H-6), 7.55 (1H, ddd, *J* = 1.4, 8.3 and 8.4 Hz, H-7), 7.91 (1H, dd, *J* = 1.4 and 8.3 Hz, H-8), 7.73 (1H, d, *J* = 9.6 Hz, H-9), 7.62 (1H, d, *J* = 9.6 Hz, H-10); ^{13}C NMR δ 116.7 (C-1), 154.2 (C-2), 111.8 (C-3), 124.5 (C-4), 122.1 (C-5), 126.0 (C-6), 126.7 (C-7), 128.6 (C-8), 127.7 (C-9), 125.6 (C-10), 133.8 (C-1a), 124.7 (C-4a), 130.6 (C-5a), 131.3 (C-8a).

*Synthesis of 2-Hydroxy-7-methyl-9,10-dihydrophenanthrene (**7h**) and 2-Hydroxy-7-methylphenanthrene (**8h**).* A solution of **1** (3 mmol) and 4-iodotoluene (3 mmol) in dry DMF (5 ml) was added to the mixture of the active nickel complex prepared as above reported. Work-up after 9 hr at 35°C and chromatography on silica gel (benzene–Et_2O 19 : 1) gave biaryl **5d** (266 mg, 1.1 mmol, 37%): ^{1}H NMR δ 6.97 (1H, dd, *J* = 2.7 and 8.4 Hz, H-5), 7.24–7.35 (6H, m, H-3, H-6, H-2′–H-6′), 5.11 (1H, q, *J* = 6.5 Hz, H-7), 1.50 (3H, d, *J* = 6.5 Hz, H-8), 2.52 (3H, s, Me), 3.98 (3H, s, OMe); ^{13}C NMR δ 132.5 (C-1), 144.7 (C-2), 110.6 (C-3), 159.4 (C-4), 113.1 (C-5), 131.3 (C-6), 66.6 (C-7), 25.1 (C-8), 55.4 (OMe), 137.9 (C-1′) 128.7 (C-2′ and C-6′), 129.8 (C-3′ and C-5′), 136.5 (C-4′).

Dehydration by I_2 of **5d** for 6 hr at 140°C and chromatography as reported gave **6d** (198 mg, 0.8 mmol, 73%): ^{1}H NMR δ 6.94 (1H, dd, *J* = 2.6 and 8.4 Hz, H-5), 7.22–7.35 (6H, m, H-3, H-6, H-2′–H-6′), 6.78 (1H, dd, *J* = 11.0 and 17.5 Hz, H-7), 5.76 (1H, dd, *J* = 1.3 and 17.5 Hz, H-8), 5.25 (1H, dd, *J* = 1.3 and 11.0 Hz, H-8), 2.45 (3H, s, Me), 3.91 (3H, s, OMe); ^{13}C NMR δ 133.8 (C-1), 136.9 (C-2), 110.6 (C-3), 158.9 (C-4), 113.6 (C-5), 131.2 (C-6), 136.1 (C-7), 114.6 (C-8), 55.3 (OMe), 137.7 (C-1′), 128.7 (C-2′ and C-6′), 129.8 (C-3′ and C-5′), 136.3 (C-4′), 21.1 (Me).

Photocyclization of **6d** (99 mg, 0.4 mmol) in the absence and in presence of atmospheric oxygen, as reported above, gave 7-methyl-2-methoxy-9,10-dihydrophenathrene (**7g**) (74 mg, 0.3 mmol, 75%) and 7-methyl-2-methoxyphenanthrene (**8g**) (50 mg, 0.2 mmol, 50%). **7g** had: ^{1}H NMR δ 6.79 (1H, d, *J* 2.1 Hz, H-1), 6.85 (1H, dd, *J* = 2.1 and 8.2 Hz, H-3), 7.65 (1H, d, *J* = 8.2 Hz, H-4), 7.58 (1H, d, *J* = 7.9 Hz, H-5), 7.10 (1H, dd, *J* = 2.0 and 7.9 Hz, H-6), 7.04 (1H, d, *J* = 2.0 Hz, H-8), 2.84 (4H, brs, H-9 and H-10), 2.36 (3H, s, Me), 3.85 (3H, s, OMe); ^{13}C NMR δ 112.2 (C-1), 158.7 (C-2), 113.4 (C-3), 124.9 (C-4), 123.2 (C-5), 127.7 (C-6), 136.5 (C-7), 129.0 (C-8), 29.5 (C-9), 29.7 (C-10), 139.1 (C-1a), 128.2 (C-4a), 131.7 (C-5a), 136.5 (C-8a), 21.3 (Me), 55.2 (OMe). **8g** had: ^{1}H NMR δ 7.25 (1H, d, *J* = 1.4 Hz, H-1), 7.28 (1H, dd, *J* = 1.4 and 8.4 Hz, H-3), 8.55 (1H, d, *J* = 8.4 Hz, H-4), 8.48 (1H, d, *J* = 8.4 Hz, H-5), 7.47 (1H, dd, *J* = 1.4 and 8.4 Hz, H-6), 7.64 (1H, d, *J* = 1.4 Hz, H-8), 7.66 (2H, d, *J* = 9.4 Hz, H-9 and H-10), 2.53 (3H, s, Me), 3.94 (3H, s, OMe); ^{13}C NMR δ 117.0 (C-1), 158.0 (C-2), 108.6 (C-3), 124.1 (C-4), 122.1 (C-5), 127.3 (C-6),

135.2 (C-7), 128.5 (C-8), 127.3 (C-9), 126.5 (C-10), 133.1 (C-1a), 124.8 (C-4a), 128.8 (C-5a), 131.2 (C-8a), 21.4 (Me), 55.4 (OMe).

BBr_3 demethylation of **7g** gave **7h** (60 mg, 35%): ^{1}H NMR δ 6.71 (1H, d, J = 2.1 Hz, H-1), 6.77 (1H, dd, J = 2.1 and 8.2 Hz, H-3), 7.61 (1H, d, J = 8.2 Hz, H-4), 7.57 (1H, d, J = 7.9 Hz, H-5), 7.10 (1H, dd, J = 2.0 and 7.9 Hz, H-6), 7.05 (1H, d, J = 2.0 Hz, H-8), 2.82 (4H, brs, H-9 and H-10), 2.36 (3H, s, Me); ^{13}C NMR δ 114.0 (C-1), 154.9 (C-2), 115.2 (C-3), 125.1 (C-4), 123.2 (C-5), 127.9 (C-6), 136.7 (C-7), 129.1 (C-8), 29.3 (C-9), 29.6 (C-10), 139.4 (C-1a), 128.0 (C-4a), 131.9 (C-5a), 136.6 (C-8a), and 21.4 (Me). Demethylation by BBr_3 of **8g** gave **8h** (43 mg, 90%): ^{1}H NMR δ 7.23 (1H, d, J = 1.4 Hz, H-1), 7.21 (1H, dd, J = 1.4 and 8.3 Hz, H-3), 8.54 (1H, d, J = 8.3 Hz, H-4), 8.46 (1H, d, J = 8.3 Hz, H-5), 7.47 (1H, dd, J = 1.6 and 8.5 Hz, H-6), 7.64 (1H, d, J = 1.6 Hz, H-8), 7.64 (1H, d, J = 9.6 Hz, H-9), 7.58 (1H, d, J = 9.6 Hz, H-10), 2.56 (3H, s, Me); ^{13}C NMR δ 116.6 (C-1), 153.9 (C-2), 111.7 (C-3), 124.3 (C-4), 122.0 (C-5), 127.5 (C-6), 135.3 (C-7), 128.5 (C-8), 127.5 (C-9), 126.0 (C-10), 133.1 (C-1a), 125.0 (C-4a), 128.3 (C-5a), 131.1 (C-8a), 21.4 (Me).

*Synthesis of 2-Hydroxy-5-methyl-9,10-dihydrophenanthrene (**7d**) and 2-Hydroxy-5-methylphenanthrene (**8d**).* 2-Iodo-5-methoxyacetophenone, obtained by reaction of equimolar amounts of 3-methoxyacetophenone (**3**), I_2, and CF_3COOAg, was cross-coupled with 2-iodotoluene for 70 hr at 40°C as reported above to give the corresponding biaryl: ^{1}H NMR δ 6.93 (1H, dd, J = 2.1 and 8.4 Hz, H-5), 7.10–7.32 (6H, m, H-3, H-6, H-3′–H-6′), 2.15 (3H, s, H-8), 1.95 (3H, s, Me), 3.90 (3H, s, OMe); ^{13}C NMR δ 136.0 (C-1), 136.0 (C-2), 112.3 (C-3), 158.8 (C-4), 117.3 (C-5), 130.3 (C-6), 203.1 (C-7), 29.8 (C-8), 55.6 (OMe), 141.2 (C-1′), 140.5 (C-2′), 130.0 (C-3′), 127.9 (C-4′), 125.9 (C-5′), 130.3 (C-6′), 20.2 (Me).

$NaBH_4$ reduction of biaryl gave a crude product that was directly dehydrated by I_2 in xylene to the vinyl intermediate **6b**: ^{1}H NMR δ 6.90 (1H, dd, J = 2.6 and 8.4 Hz, H-5), 7.07–7.29 (6H, m, H-3, H-6, H-3′–H-6′), 6.41 (1H, dd, J = 10.8 and 17.0 Hz, H-7), 5.66 (1H, dd, J = 1.3 and 17.0 Hz, H-8), 5.13 (1H, dd, J = 1.3 and 10.8 Hz, H-8), 2.08 (3H, s, Me), 3.91 (3H, s, OMe); ^{13}C NMR δ 133.6 (C-1), 137.0 (C-2), 109.7 (C-3), 158.8 (C-4), 113.5 (C-5), 131.0 (C-6), 135.2 (C-7), 114.5 (C-8), 55.4 (OMe), 140.4 (C-1′), 140.0 (C-2′), 129.8 (C-3′), 127.3 (C-4′), 125.5 (C-5′), 130.3 (C-6′), 20.1 (Me).

Photocyclization of **6b** in both the reported conditions gave 2-methoxy-5-methyl-9,10-dihydrophenanthrene (**7c**) and 2-methoxy-5-methylphenanthrene (**8c**). **7c** had: ^{1}H NMR δ 6.87 (1H, d, J = 2.2 Hz, H-1), 6.85 (1H, dd, J = 2.2 and 8.4 Hz, H-3), 7.63 (1H, d, J = 8.4 Hz, H-4), 7.13–7.15 (3H, m, H-6, H-7, and H-8), 2.76 (4H, brs, H-9 and H-10), 2.62 (3H, s, Me), 3.87 (3H, s, OMe); ^{13}C NMR δ 110.9 (C-1), 158.3 (C-2), 113.3 (C-3), 130.6 (C-4), 133.9 (C-5), 129.4 (C-6), 125.5 (C-7), 126.1 (C-8), 30.8 (C-9), 30.5 (C-10), 139.2 (C-1a), 127.7 (C-4a), 140.8 (C-5a), 134.1 (C-8a), 23.1 (Me), 55.3 (OMe). **8c** had: ^{1}H NMR δ

7.29 (1H, d, J = 1.4 Hz, H-1), 7.28 (1H, dd, J = 1.4 and 8.4 Hz, H-3), 8.59 (1H, d, J = 8.4 Hz, H-4), 7.47 (1H, dd, J = 1.4 and 8.3 Hz, H-6), 7.32 (1H, ddd, J = 1.4, 8.3 and 8.4 Hz, H-7), 7.76 (1H, dd, J = 1.4 and 8.4 Hz, H-8), 7.69 (2H, d, J = 9.4 Hz, H-9 and H-10), 3.12 (3H, s, Me), 4.00 (3H, s, OMe); ^{13}C NMR δ 115.5 (C-1), 159.7 (C-2), 109.1 (C-3), 131.3 (C-4), 135.0 (C-5), 129.0 (C-6), 128.7 (C-7), 125.0 (C-8), 127.6 (C-9), 126.7 (C-10), 133.0 (C-1a), 124.2 (C-4a), 134.3 (C-5a), 131.3 (C-8a), 27.4 (Me), 55.4 (OMe).

BBr_3 demethylation of **7c** and **8c** gave **7d** and **8d**, respectively. **7d** had: ^{1}H NMR δ 6.79 (1H, d, J = 2.3 Hz, H-1), 6.78 (1H, dd, J = 2.3 and 8.4 Hz, H-3), 7.48 (1H, d, J = 8.4 Hz, H-4), 7.13–7.15 (3H, m, H-6, H-7, and H-8), 2.73 (4H, brs, H-9 and H-10), 2.61 (3H, s, Me); ^{13}C NMR δ 112.4 (C-1), 154.0 (C-2), 114.4 (C-3), 130.4 (C-4), 133.8 (C-5), 129.5 (C-6), 125.4 (C-7), 125.9 (C-8), 30.6 (C-9), 29.7 (C-10), 139.0 (C-1a), 127.7 (C-4a), 141.9 (C-5a), 134.0 (C-8a), 23.0 (Me). **8d** had: ^{1}H NMR δ 7.28 (1H, d, J = 1.5 Hz, H-1), 7.24 (1H, dd, J = 1.5 and 8.4 Hz, H-3), 8.59 (1H, d, J = 8.4 Hz, H-4), 7.47 (1H, dd, J = 1.4 and 8.3 Hz, H-6), 7.30 (1H, ddd, J = 1.4, 8.3 and 8.4 Hz, H-7), 7.74 (1H, dd, J = 1.4 and 8.4 Hz, H-8), 7.69 (1H, d, J = 9.4 Hz, H-9), 7.56 (1H, d, J = 9.4 Hz, H-10), 3.11 (3H, s, Me); ^{13}C NMR δ 115.2 (C-1), 153.3 (C-2), 112.1 (C-3), 131.3 (C-4), 135.8 (C-5), 129.3 (C-6), 128.6 (C-7), 125.1 (C-8), 127.6 (C-9), 125.2 (C-10), 132.8 (C-1a), 122.1 (C-4a), 134.6 (C-5a), 131.8 (C-8a), 27.8 (Me).

*Synthesis of 2-Hydroxy-6-methyl-9,10-dihydrophenanthrene (**7f**), 2-Hydroxy-8-methyl-9,10-dihydrophenanthrene (**7l**), 2-Hydroxy-6-methylphenanthrene (**8f**), and 2-Hydroxy-8-methylphenanthrene (**8l**).* Equimolar amounts of **1** (6 mmol) and 3-iodotoluene were cross-coupled as described for **7h** at 40°C to give biaryl **5c**: ^{1}H NMR δ 7.38 (1H, d, J = 2.7 Hz, H-3), 7.03 (1H, dd, J = 2.7 and 8.4 Hz, H-5), 7.30 (1H, d, J = 8.4 Hz, H-6), 7.24–7.50 (4H, m, H-2′–H-6′), 5.15 (1H, q, J = 6.4 Hz, H-7), 1.58 (3H, d, J = 6.4 Hz, H-8), 2.57 (3H, s, Me), 4.04 (3H, s, OMe); ^{13}C NMR δ 133.0 (C-1), 144.6 (C-2), 110.3 (C-3), 159.4 (C-4), 112.9 (C-5), 131.1 (C-6), 66.4 (C-7), 25.1 (C-8), 55.3 (OMe), 140.7 (C-1′), 128.0 (C-2′), 137.6 (C-3′), 127.6 (C-4′), 130.3 (C-5′), 126.6 (C-6′), 21.4 (Me).

Dehydration of **5c** gave biaryl **6c**: ^{1}H NMR δ 6.90 (1H, dd, J = 2.3 and 8.3 Hz, H-5), 7.08–7.29 (6H, m, H-3, H-6, H-2′–H-6′), 6.42 (1H, dd, J = 11.0 and 17.1 Hz, H-7), 5.13 (1H, dd, J = 2.0 and 11.0 Hz, H-8), 5.61 (1H, dd, J = 2.0 and 17.1 Hz, H-8), 2.08 (3H, s, Me), 3.91 (3H, s, OMe); ^{13}C NMR δ 133.9 (C-1), 136.8 (C-2), 109.7 (C-3), 158.8 (C-4), 113.5 (C-5), 131.0 (C-6), 135.2 (C-7), 114.5 (C-8), 55.4 (OMe), 140.4 (C-1′), 127.8 (C-2′), 137.5 (C-3′), 127.3 (C-4′), 130.6 (C-5′), 127.0 (C-6′), 20.1 (Me).

Photocyclization of **6c** under argon gave a mixture of 2-methoxy-6-methyl-9,10-dihydrophenanthrene (**7e**) and 2-methoxy-8-methyl-9,10-dihydrophenanthrene (**7i**) which was separated by HPLC-NH_2 (isopropyl ether–hexane 1 : 49). **7e** had: ^{1}H NMR δ 6.79 (1H, d, J = 2.3 Hz, H-1), 6.84 (1H, dd, J = 2.3 and 8.3 Hz, H-3), 7.68 (1H, d, J = 8.3 Hz, H-4), 7.51 (1H, d, J = 2.1 Hz, H-5), 7.00

(1H, dd, *J* = 2.1 and 7.7 Hz, H-7), 7.12 (1H, d, *J* = 7.7 Hz, H-8), 2.84 (4H, brs, H-9 and H-10), 2.40 (3H, s, Me), 3.85 (3H, s, OMe); ^{13}C NMR δ 112.3 (C-1), 158.9 (C-2), 113.5 (C-3), 124.9 (C-4), 124.9 (C-5), 134.2 (C-6), 127.9 (C-7), 127.3 (C-8), 29.7 (C-9), 28.7 (C-10), 139.2 (C-1a), 128.6 (C-4a), 136.2 (C-5a), 133.3 (C-8a), 21.4 (Me), 55.3 (OMe). **7i** had: ^{1}H NMR δ 6.83 (1H, d, *J* = 2.2 Hz, H-1), 6.88 (1H, dd, *J* = 2.2 and 8.2 Hz, H-3), 7.74 (1H, d, *J* = 8.2 Hz, H-4), 7.61 (1H, d, *J* = 7.8 Hz, H-5), 7.23 (1H, dd, *J* = 7.8 and 7.8 Hz, H-6), 7.12 (1H, d, *J* = 7.8 Hz, H-7), 2.87 (4H, brs, H-9 and H-10), 2.39 (3H, s, Me), 3.85 (3H, s, OMe); ^{13}C NMR δ 112.3 (C-1), 158.4 (C-2), 113.2 (C-3), 125.3 (C-4), 121.1 (C-5), 126.3 (C-6), 128.5 (C-7), 135.1 (C-8), 24.7 (C-9), 29.1 (C-10), 138.7 (C-1a), 127.8 (C-4a), 135.2 (C-5a), 134.8 (C-8a), 19.9 (Me), 55.3 (OMe).

BBr_3 demethylation of **7e** and **7i** gave **7f** and **7l**. **7f** had: ^{1}H NMR δ 6.73 (1H, d, *J* = 2.3 Hz, H-1), 6.78 (1H, dd, *J* = 2.3 and 8.3 Hz, H-3), 7.65 (1H, d, *J* = 8.3 Hz, H-4), 7.51 (1H, d, *J* = 2.1 Hz, H-5), 7.00 (1H, dd, *J* = 2.1 and 7.7 Hz, H-7), 7.13 (1H, d, *J* = 7.7 Hz, H-8), 2.82 (4H, brs, H-9 and H-10), 2.40 (3H, s, Me); ^{13}C NMR δ 113.7 (C-1), 154.8 (C-2), 114.9 (C-3), 125.0 (C-4), 125.5 (C-5), 134.1 (C-6), 127.9 (C-7), 127.2 (C-8), 29.8 (C-9), 28.9 (C-10), 139.5 (C-1a), 128.5 (C-4a), 136.3 (C-5a), 133.4 (C-8a), 21.7 (Me). 2-Hydroxy-8-methyl-9,10-dihydrophenanthrene (**7l**) had: ^{1}H NMR δ 6.73 (1H, d, *J* = 2.2 Hz, H-1), 6.79 (1H, dd, *J* = 2.2 and 8.2 Hz, H-3), 7.63 (1H, d, *J* = 8.2 Hz, H-4), 7.57 (1H, d, *J* = 7.6 Hz, H-5), 7.21 (1H, dd, *J* = 7.6 and 7.9 Hz, H-6), 7.10 (1H, d, *J* = 7.9 Hz, H-7), 2.80 (4H, brs, H-9 and H-10), 2.35 (3H, s, Me); ^{13}C NMR δ 114.1 (C-1), 155.1 (C-2), 114.9 (C-3), 125.9 (C-4), 121.3 (C-5), 126.6 (C-6), 128.9 (C-7), 135.3 (C-8), 24.9 (C-9), 29.2 (C-10), 139.4 (C-1a), 128.3 (C-4a), 135.6 (C-5a), 134.6 (C-8a), 20.2 (Me).

Photocyclization in the presence of oxygen atmosphere followed by HPLC-NH_2 gave 2-methoxy-6-methylphenanthrene (**8e**) and 2-methoxy-8-methylphenanthrene (**8i**). **8e** had: ^{1}H NMR δ 7.29 (1H, d, *J* = 1.4 Hz, H-1), 7.28 (1H, dd, *J* = 1.4 and 8.4 Hz, H-3), 8.62 (1H, d, *J* = 8.4 Hz, H-4), 8.41 (1H, d, *J* = 1.5 Hz, H-5), 7.43 (1H, dd, *J* = 1.5 and 8.4 Hz, H-7), 7.68 (1H, d, *J* = 8.4 Hz, H-8), 7.76 (2H, d, *J* = 9.4 Hz, H-9 and H-10), 2.64 (3H, s, Me), 3.99 (3H, s, OMe); ^{13}C NMR δ 117.3 (C-1), 158.3 (C-2), 108.6 (C-3), 124.3 (C-4), 123.5 (C-5), 134.9 (C-6), 126.9 (C-7), 128.5 (C-8), 126.4 (C-9), 125.6 (C-10), 133.8 (C-1a), 123.5 (C-4a), 130.5 (C-5a), 128.2 (C-8a), 22.2 (Me), 55.4 (OMe). **8i** had: ^{1}H NMR δ 7.25 (1H, d, *J* = 1.4 Hz, H-1), 7.27 (1H, dd, *J* = 1.4 and 8.4 Hz, H-3), 8.62 (1H, d, *J* = 8.4 Hz, H-4), 8.51 (1H, dd, *J* = 1.5 and 8.4 Hz, H-5), 7.52 (1H, ddd, *J* = 1.5, 8.4 and 8.4 Hz, H-6), 7.37 (1H, dd, *J* = 1.5 and 8.4 Hz, H-7), 7.95 (1H, d, *J* = 9.4 Hz, H-9), 7.73 (1H, d, *J* = 9.4 Hz, H-10), 2.76 (3H, s, Me), 3.98 (3H, s, OMe); ^{13}C NMR δ 116.9 (C-1), 158.3 (C-2), 108.4 (C-3), 124.7 (C-4), 120.5 (C-5), 126.3 (C-6), 127.7 (C-7), 136.3 (C-8), 122.0 (C-9), 125.6 (C-10), 133.8 (C-1a), 123.5 (C-4a), 129.8 (C-5a), 133.8 (C-8a), 20.0 (Me), 55.4 (OMe).

BBr_3 demethylation of **8e** and **8i** afforded **8f** and **8l**. **8f** had: ^{1}H NMR δ

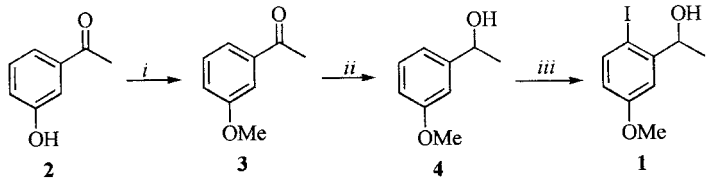
7.27 (1H, d, J = 1.5 Hz, H-1), 7.24 (1H, dd, J = 1.5 and 8.3 Hz, H-3), 8.61 (1H, d, J = 8.3 Hz, H-4), 8.38 (1H, d, J = 1.6 Hz, H-5), 7.39 (1H, dd, J = 1.6 and 8.3 Hz, H-7), 7.72 (1H, d, J = 8.3 Hz, H-8), 7.68 (1H, d, J = 9.6 Hz, H-9), 7.55 (1H, d, J = 9.6 Hz, H-10), 2.63 (3H, s, Me); ^{13}C NMR δ 117.7 (C-1), 156.1 (C-2), 111.2 (C-3), 124.2 (C-4), 123.0 (C-5), 134.7 (C-6), 126.9 (C-7), 128.3 (C-8), 126.3 (C-9), 125.2 (C-10), 133.7 (C-1a), 123.9 (C-4a), 130.9 (C-5a), 129.1 (C-8a), 22.1 (Me). **8l** had: ^{1}H NMR δ 7.23 (1H, d, J = 1.4 Hz, H-1), 7.21 (1H, dd, J = 1.4 and 8.3 Hz, H-3), 8.56 (1H, d, J = 8.3 Hz, H-4), 8.47 (1H, dd, J = 1.5 and 8.3 Hz, H-5), 7.50 (1H, ddd, J = 1.5, 8.3, and 8.5 Hz, H-6), 7.34 (1H, dd, J = 1.5 and 8.3 Hz, H-7), 7.90 (1H, d, J = 9.5 Hz, H-9), 7.63 (1H, d, J = 9.5 Hz, H-10), 2.75 (3H, s, Me); ^{13}C NMR δ 116.8 (C-1), 156.6 (C-2), 111.1 (C-3), 124.5 (C-4), 120.2 (C-5), 126.1 (C-6), 127.0 (C-7), 136.4 (C-8), 121.5 (C-9), 125.9 (C-10), 133.7 (C-1a), 123.9 (C-4a), 129.7 (C-5a), 134.2 (C-8a), 20.5 (Me).

Bioassay. The strain UTEX 1648 of *Selenastrum capricornutum* was maintained on Bold basal medium (BBM) (Nichols, 1973) solidified with 1.5% agar in continuous light at 23°C. Fresh axenic cultures for the experiments were grown in 100-ml cylinders on the same culture medium. For the growth tests, the compounds were dissolved in acetone. Each solution (20 μl) was added to the test tubes containing 6 ml of inoculated medium, giving final concentrations of 10^{-4}, 5×10^{-5} and 10^{-5} M. Blanks containing only acetone were also tested. The test tubes were incubated at 23°C on a shaking apparatus previously described (Aliotta et al., 1991). The total irradiation of 150 μE/sec/m^2 was provided by daylight fluorescent lamps (Philips TLD 30 w/55) from below the apparatus. The photoperiod was 16 hr light–8 hr dark. Growth of cultures was followed daily either by measuring the absorbance increase at 550 nm with a Bausch & Lomb Spectronic 20 colorimeter or by counting the cell numbers with a Thoma blood-counting chamber. The cell numbers of the initial inocula ranged from 10^6 to 1.5×10^6/ml, corresponding to 0.05–0.06 units of absorbance. Growth experiments were carried out in triplicate. To test statistical significance of results, one-way ANOVA was performed at P = 0.05. For each compound, a comparison among means was performed by using the Student-Newman-Keuls test (SNK), at P = 0.05. The SPSS statistical package was used.

The index of inhibition for compounds was calculated as: $[(1 - X_a)/Y_a] \times 100$ (Blankley, 1973), where X_a is the growth-rate of the alga in the presence of the compound tested and Y_a is the growth rate of the control.

RESULTS AND DISCUSSION

The building block 1-(2-iodo-5-methoxy)-phenylethanol (**1**) was obtained with an overall 90% yield from 3-hydroxyacetophenone (**2**) (Scheme 1). Commercially available (Sigma) **2** was converted into its *O*-methyl derivative **3** by



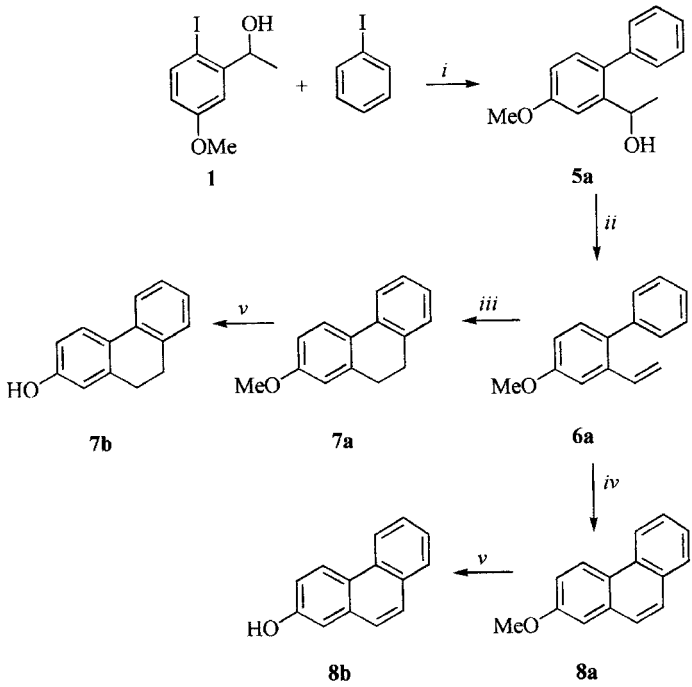
SCHEME 1. Synthesis of **1**. i: Me_2SO_4, NaOH, EtOH; ii: $NaBH_4$, MeOH; iii: I_2, CF_3COOAg, CH_2Cl_2.

Me_2SO_4, and $NaBH_4$ reduction of this latter gives 1-(3-methoxy)-phenylethanol (**4**), which, by treatment with I_2 and CF_3COOAg, afforded the target.

In the first synthesis, 1-(2-iodo-5-methoxy)-phenylethanol (**1**) was cross-coupled with iodobenzene. The nickel catalyzed homo- and hetero-coupling of aryl halides has been extensively studied (Tiecco et al., 1984) and has been found to be dependent on the selection of zero valent nickel complexes, solvents, the nature of the halides, and additives such as PPh_3 or Et_4NI.

The coupling was investigated under the conditions reported. The best results were obtained in DMF when equimolar amounts of 1-(2-iodo-5-methoxy)-phenylethanol (**1**) and iodobenzene were added at once to a reaction mixture containing the active nickel complex (Scheme 2). The complex was formed by zinc reduction of $NiCl_2(PPh_3)_2$, generated in situ from $NiCl_2$ and PPh_3 in a 1 : 4 ratio. Under such conditions, the asymmetric biaryl 1-(5-methoxy-2-phenyl)-phenylethanol (**5a**) was obtained in 47% yield along with minor amounts of the symmetric biaryls. Biaryl **5a** was then dehydrated to 5-methoxy-2-phenylstyrene (**6a**) in 86% yield by warming at 140°C in dry xylene with I_2 for 6 hr. The vinyl derivative **6a** was then photocyclized to 2-methoxy-9,10-dihydrophenanthrene (**7a**) by irradiation (Padwa et al., 1977) with a 450-W Hanovia Lamp. The best yields of conversion of **6a** to **7a** were achieved when irradiation was run in dry benzene at room temperature for 1 hr under argon. In such cases about 50% of **6a** was recovered from the reaction mixture, and the only product obtained was **7a**. At longer reaction times a series of byproducts was formed. An overall 87% conversion yield of **6a** to **7a** was obtained after two photocyclization reactions. When the reaction was run in the presence of atmospheric oxygen under the same conditions, 2-methoxyphenanthrene (**8a**) in overall 82% yield was formed along with small amounts of **7a** (5%). Finally **7a** and **8a** were demethylated by BBr_3 in CH_2Cl_2 for 3 hr at −70°C to afford 2-hydroxy-9,10-dihydrophenanthrene (**7b**) and 2-hydroxyphenanthrene (**8b**) in 70 and 73% yields, respectively.

2-Hydroxy-7-methylphenathrene (**8h**) and its 9,10-dihydro analog (**7h**) were obtained in the same way starting from 4-iodotoluene: the biaryl **5d**, obtained in 37% yield in the coupling, was dehydrated to the vinyl derivative



SCHEME 2. Synthesis of 2-hydroxy-9,10-dihydrophenanthrene (**7b**) and 2-hydroxyphenanthrene (**8b**). i: Zn, PPh_3, $NiCl_2$, DMF; ii: I_2, xylene; iii: hν, benzene, Ar; iv: hν, benzene, air; v: BBr_3, CH_2Cl_2.

6d (78% yields); photocyclization in absence and in the presence of oxygen gave 2-methoxy-7-methyl-9,10-dihydrophenathrene (**7g**) (75%) and 2-methoxy-7-methylphenanthrene (**8g**) (50%), which were demethylated to furnish **7h** and **8h** in 85% and 90% yields, respectively.

2-Hydroxy-6-methyl-9,10-dihydrophenanthrene (**7f**) and 2-hydroxy-8-methyl-9,10-dihydrophenanthrene (**7l**), as well as the corresponding 2-hydroxy-6-methylphenathrene (**8f**) and 2-hydroxy-8-methylphenanthrene (**8l**), were obtained in the cross-coupling of 3-iodotoluene with **1**. The asymmetric biaryl **5c**, obtained in 38% yield, was dehydrated to the vinyl intermediate **6c**. The photocyclization of the latter under argon gave a mixture of 2-methoxy-6-methyl- (**7e**) and 2-methoxy-8-methyl-9,10-dihydrophenanthrene (**7i**). In contrast, 2-methoxy-6-methyl (**8e**) and 2-methoxy-8-methylphenanthrene (**8i**) were formed in the presence of oxygen. The predominance in both cases of the 6-methyl isomers **7e** and **8e** may be explained on steric grounds. The mixtures were resolved by HPLC. Demethylation of the pure methoxyderivatives by BBr_3

afforded the targets **7f**, **7l**, **8f**, and **8l** in overall 11%, 8%, 13%, and 9% yields, respectively.

When **1** was coupled with 2-iodotoluene in the synthesis of 2-hydroxy-5-methyl-9,10-dihydrophenanthrene (**7d**) and the corresponding phenanthrene **8d**, the only products formed were toluene and **3**. As reported by Semmelhack et al. (1981), the coupling of sterically hindered 2-halotoluenes requires long times, and, under the present conditions, the primary process was the replacement of iodide by the alcoholic hydrogen of **1**. Compounds **7d** and **8d** were obtained starting from 2-iodo-5-methoxyacetophenone, which was coupled with 2-iodotoluene. The reaction was run at 40°C for 70 hr to give the corresponding asymmetric biaryl in 26% yield. Reduction by $NaBH_4$ and dehydration afforded the vinyl intermediate **6b**. Photocyclization in both conditions afforded 2-methoxy-5-methyl-9,10-dihydrophenanthrene (**7c**) and the corresponding phenanthrene **8c**, which, by demethylation, were converted to the targets **7d** and **8d**.

The 2-hydroxy-9,10-dihydrophenanthrenes, the 2-hydroxyphenathrenes, and the corresponding *O*-methyl derivatives were assayed in broth against *Selenastrum capricornutum* at concentrations of 10^{-4}–10^{-5} M, the range usually used with commercial algicides. All compounds were purified by HPLC before the tests and were found to be stable under the conditions of the assay. The statistical significance of results and the index of inhibition were calculated.

All compounds, except 2-methoxy-7-methylphenanthrene (**8g**), had strong activity at 10^{-4} M, with inhibition higher than 70% (Tables 1 and 2). The most active were dihydrophenathrenes **7a, 7b, 7c, 7e,** and **7i** and the phenathrenes **8c** and **8d**, which caused full inhibition of algal growth. At the lowest concentration, all compounds, except the dihydrophenathrenes **7d, 7g, 7h,** and **7l** and the phenathrenes **8a, 8b, 8c,** and **8g,** retained strong activity. Dihydrophenanthrenes **7b, 7c, 7e,** and **7i** and phenanthrene **8d** fully inhibited the algal growth.

TABLE 1. INHIBITION OF *S. capricornutum* GROWTH BY SYNTHETIC 9,10-DIHYDROPHENANTHRENES[a]

	Inhibition (%)									
	7b	**7a**	**7d**	**7c**	**7f**	**7e**	**7h**	**7g**	**7l**	**7i**
10^{-4} M	96b	98c	86b	95b	91b	100b	80d	92c	77b	98b
5×10^{-5} M	96b	93b	86b	95b	91b	100b	75c	92c	77b	98b
10^{-5} M	96b	93b	0a	95b	91b	100b	48b	20b	0a	98b
Control	0a	0a	0a	0a	0a	0a	0a	0a	0a	0a

[a]In each column values followed by different letters are statistically significant. Student-Newman-Keuls test; $P = 0.05$.

TABLE 2. INHIBITION OF *S. capricornutum* GROWTH BY SYNTHETIC PHENANTHRENES

	Inhibition (%)									
	8b	**8a**	**8d**	**8c**	**8f**	**8e**	**8h**	**8g**	**8l**	**8i**
10^{-4} M	72c	80d	95b	97c	85c	90b	80b	10b	85c	90b
5×10^{-5} M	72c	76c	95b	97c	80b	90b	80b	10b	80b	90b
10^{-5} M	47b	69b	95b	20b	80b	90b	80b	0a	80b	90b
Control	0a	0a	0a	0a	0a	0a	0a	0a	0a	0a

[a]In each column values followed by different letters are statistically significant. Student-Newman-Keuls test; $P = 0.05$.

The methoxyderivatives are more active than hydroxyderivatives in the dihydrophenanthrene series, while in the phenanthrene series their activities are comparable. The introduction of a methyl in the C ring of methoxydihydrophenanthrenes did not change the activity, while a reduction was observed in the hydroxydihydrophenanthrenes. The activity increased in all the hydroxyphenathrenes and in the substituted methoxyphenanthrenes, except for 2-methoxy-7-methylphenanthrene, which was inactive for all concentrations.

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