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Phytotoxic Activity of Quinones and Resorcinolic Lipid Derivatives

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On the basis of the reported phytotoxic activity of sorgoleone and resorcinolic lipids identified from the root extracts of *Sorghum bicolor*, 8 resorcinolic lipid derivatives and 10 quinones with various side chain sizes were synthesized. The phytotoxicity of the compounds was tested against a monocot and a dicot species. The quinones were phytotoxic, whereas the resorcinolic lipids were not. Of the quinones, 2-hydroxy-5-methoxy-3-pentylcyclohexa-2,5-diene-1,4-dione, having a five-carbon side chain, showed phytotoxic activity similar to that of natural compound sorgoleone.

KEYWORDS: Sorgoleone; resorcinols; quinones; phytotoxic

INTRODUCTION

Every year about 13% of the world's crops are lost due to damages caused by weed. The development of weed control technology such as transgenic crops and synthetic herbicides has made a great contribution to the improvement of crop yields through the years. According to Bridges (*1*, *2*) losses in agricultural production would be 500% higher without the use of herbicides. However, herbicide resistance and the sensitivity of the public to the use of synthetic herbicides for food production leave a place in the market for safer and more efficacious herbicides.

Allelopathy is the inhibition of growth of a plant through the production of phytotoxins released by another plant. This phenomenon represents warfare between neighboring plants competing for light, water, and nutrients (*3*, *4*). There are several crop plants in which allelopathic effects have been observed, including rice, wheat, oats, sunflower, barley, and sorghum, with rice being the most studied case.

Sorghum is considered to be one of the most important cereal crops in the world (*5*). The allelopathic activity of this plant was noticed due to the significant reduction of growth of other crops when grown in rotation with sorghum (*6*).

Sorgoleone (**1**, **Figure 1**) is a natural quinone released from sorghum root exudates. The ability of sorghum crops to inhibit the growth of weeds is attributed to sorgoleone. For this reason, *Sorghum* species are used sometimes as cover crops in the southern parts of the United States (*7*). The allelopathic activity of sorgoleone has been reported in a number of studies (see, e.g., refs *8* and *9*). Previous studies have also identified the resorcinolic lipid 4,6-dimethoxy-2-((8*Z*,11*Z*)-pentadeca-8′,11′,14′-trienyl)-benzene-1,3-diol (**2**, **Figure 1**) to be more phytotoxic than sorgoleone against lettuce germination (*10*). In our continuing search for natural product and natural product-based herbicides for pest management, a group of resorcinolic lipids and quinones were synthesized and tested for phytotoxicity against monocot and dicot species.

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MATERIALS AND METHODS

General Procedures for the Preparation of 26−35 (See also the Supporting Information). Preparation of quinones was accomplished according to the method of Poigny et al. (*11*). To a solution of compounds **21**−**25** (1 mmol) in acetonitrile was added ammonium cerium(IV) nitrate (2.5 mmol) dissolved in acetonitrile/water (7:3) at −7 °C. The reaction was stirred for 2 h and then ether was added. The organic layer was washed with water (3 × 10 mL), and the organic phases were combined and dried over $MgSO_4$. Removal of solvent under reduced pressure gave a crude mixture that was purified over silica gel eluting with hexanes/ethyl acetate.

2,5-Dimethoxy-3-pentylcyclohexa-2,5-diene-1,4-dione (***27***)*:* 35% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, 3H, J = 8 Hz), 1.27 (s, 4H), 1.34 (m, 2H), 2.38 (t, 2H, J = 8 Hz), 3.77 (s, 3H), 4.01 (s, 3H), 5.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 23.2, 28.5, 31.9, 56.6, 61.5, 105.5, 130.8, 156.0, 158.9, 182.6, 183.8. HRMS: calcd for $C_{13}H_{17}O_4$ [M − H] 237.1126, found 237.1130.

3-Decyl-2,5-dimethoxycyclohexa-2,5-diene-1,4-dione (***28***)*:* 32% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, 3H, J = 8 Hz), 1.23 (s, 14H), 1.37 (s, 2H), 2.41 (t, 2H, J = 8 Hz), 3.79 (s, 3H), 4.03 (s, 3H), 5.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 22.8, 23.2, 28.8, 29.5 (2C), 29.7, 29.8 (2C), 32.0, 56.5, 61.5, 105.5, 130.9, 156.0, 158.9, 182.6, 183.7. HRMS: calcd for $C_{18}H_{29}O_4$ [M + H] 309.2065, found 309.2086.

2-Hydroxy-5-methoxy-3-pentylcyclohexa-2,5-diene-1,4-dione (***32***)*:* 6.4% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, 3H, J = 8 Hz), 1.27 (s, 4H), 1.42 (t, 2H, J = 8 Hz), 2.40 (t, 2H, J = 8 Hz), 3.83 (s, 3H), 5.81 (s, 1H), 7.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 22.6, 22.7, 27.9, 31.8, 56.9, 102.4, 119.4, 151.8, 161.3, 181.9, 183.0. HRMS: calcd for $C_{12}H_{15}O_4$ [M − H] 223.0970, found 223.0966.

2-Hydroxy-5-methoxy-3-tetradecylcyclohexa-2,5-diene-1,4-dione (***35***)*:* 27% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, 3H, J = 8 Hz), 1.23 (s, 22H), 1.43 (m, 2H), 2.42 (t, 2H, J = 8 Hz), 3.84 (s, 3H), 5.82 (s, 1H), 7.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 22.8, 22.9, 28.2, 29.5, 29.6, 29.7, 29.8 (6C), 32.1, 56.9, 102.3, 119.4, 151.7, 161.3, 181.9, 183.0. HRMS: calcd for $C_{21}H_{33}O_4$ [M − H] 349.2378, found 349.2356.

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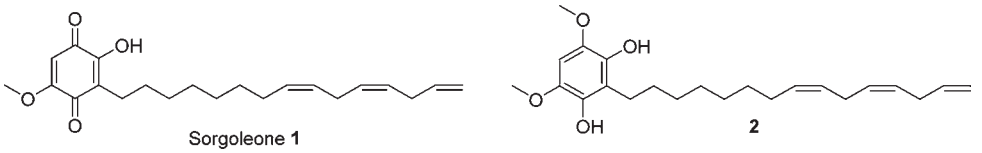


Figure 1. Chemical structures of sorgoleone (**1**) and resorcinolic lipid derivative (**2**).

Table 1. Effects of Resorcinols and Quinones on Development of Lettuce and Agrostis Seedlings[a]

compound	concentration (mM)	lettuce[b,c]	agrostis[b]
27	0.01	0	0
	0.03	0	0
	0.1	0	1
	0.3	1	3
	1	2	4
28	0.01	0	0
	0.03	0	0
	0.1	0	0
	0.3	0	0
	1	2	1
32	0.01	0	0
	0.03	0	0
	0.1	0	2
	0.3	3	3
	1	5	4
35	0.01	0	0
	0.03	0	0
	0.1	0	0
	0.3	1	0
	1	1	0
sorgoleone	0.01	0	0
	0.03	0	0
	0.1	1	0
	0.3	3	0
	1	4	0

[a] The other compounds tested (**4**−**6**, **10**−**14**, **26**, **29**−**31**, **33**, and **34**) did not show phytotoxic activity at any of the concentrations tested. [b] Ratings are based on visual inspection of growth on a scale of 0 (no activity, not phytotoxic) through 5 (highly phytotoxic, complete inhibition of seedling growth). [c] Data on phytotoxicity of sorgelone against lettuce are from Rimando et al. (*15*).

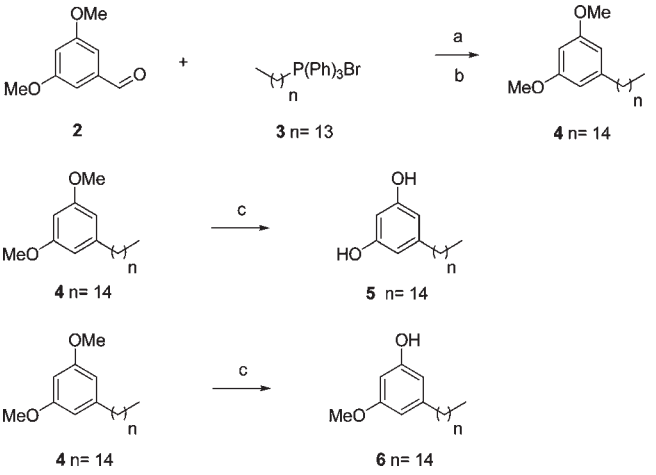
Bioassay. Lettuce seeds (*Lactuca sativa* L. cv. Iceberg A) were obtained from Burpee Seed Co. and creeping bentgrass seeds (*Agrostis stolonifera* var. Penncross) from Turf-Seed (Hubbard, OR). These species were selected because we have used them to evaluate thousands of synthetic and natural compounds for phytotoxicity with the method of Dayan et al. (*12*). Compounds were subjected to phytotoxicity assays at concentrations ranging from 0.01 to 1 mM.

RESULTS AND DISCUSSION

The activities of several resorcinols and quinones against lettuce and bentgrass growth and development are shown in **Table 1**.

Resorcinols **4**−**6** (**Scheme 1**) and **10**−**14** (**Schemes 2** and **3**) did not show any phytotoxic activity. Thus, the size of the side chain did not have any effect on toxicity. Compounds **10**, **12**, and **14**, with a side chain of 11 carbons, and compounds **6**, **11**, and **13**, with a side chain of 15 carbons, lacked activity. To study the effects that different substituents have on phytotoxicity, several alkoxy groups were introduced around the benzene ring such as acetoxy (**11** and **12**), methoxy (**4**), hydroxy (**6** and **10**), and ethoxy (**13** and **14**). Although these groups generated diversity, they did not have any growth inhibitory effect. The resorcinols and quinones synthesized in this work lack the triene unit in the side chain that the natural phytotoxic compound **1** has. Lack of activity of the resorcinols could not be due to the lack of the triene unit. Previous work has revealed that the unsaturation is not essential for biological activity (*13*, *14*). Additionally, the quinones that were found to be active in the present study did not have the triene unit.

Scheme 1[a]



[a] Reagents and conditions: (a) BuLi, THF, 12 h, room temperature; (b) Pd/C, MeOH, 12 h, room temperature; (c) BBr_3, DCM, −40 °C → room temperature, 12 h.

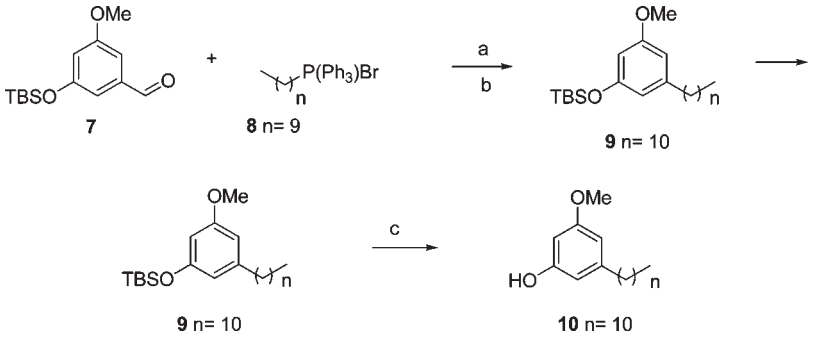
Of the quinones with side chains varying from 1 to 14 carbons (**Scheme 4**), compound **32** with a side chain of 5 carbons showed the best activity. At 0.1 mM concentration, **32** had moderate toxicity against bentgrass growth and development, and at 1.0 mM it completely inhibited the germination of lettuce (**Table 1**). This activity is very similar to that of sorgoleone as reported earlier (*15*). Compound **27**, a dimethoxylated analogue of **32**, was the second best compound, with growth inhibitory activity starting at 0.1 mM against bentgrass. At 1 mM, the development of seedlings was strongly inhibited. However, **27** showed weaker phytotoxicity against lettuce compared to **32**, even in higher concentrations. These results suggest that the hydroxyl group is preferred at the C2 position of the quinone ring for phytotoxic activity against lettuce.

Quinone **28**, which has a 10-carbon side chain, showed weak growth inhibitory activity at the highest concentration (1.0 mM) against lettuce and bentgrass. Compound **34**, the natural compound 5-*O*-methylembelin, is known to be toxic to fish (*16*). However, this compound lacked phytotoxic activity.

Previous work done by Barbosa et al. (*13*) revealed that saturation of the triene in the side chain of sorgoleone resulted in a compound with phytoxicity very similar to that of the natural compound. However compound **35**, having a 14-carbon side chain, just 1 carbon less than Barbosa's compound, had no phytotoxic activity in our studies.

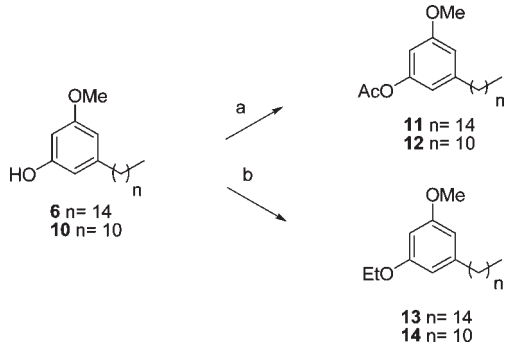
In conclusion, synthesis of resorcinols and quinones was accomplished using simple and economic synthetic procedures. The phytotoxic activity of these compounds was investigated against a monocot and a dicot species. In the present work, the

Scheme 2 [a]



[a] Reagents and conditions: (a) BuLi, THF, −78 °C→ room temperature, 12 h; (b), Pd/C, MeOH, 12 h, room temperature; (c) TBAF, THF, 45 min, room temperature.

Scheme 3 [a]



[a] Reagents and conditions: (a) acetyl chloride, TEA, DCM, 0 °C→ room temperature, 12 h; (b) EtI, K_2CO_3, DMF, room temperature, 12 h.

quinones showed better activity compared to the resorcinols. Compound **32**, the most active quinone found in this set of compounds, showed activity similar to that of the natural compound sorgoleone with the advantage of being much easier to synthesize than the natural compound.

ACKNOWLEDGMENT

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Supporting Information Available: Experimental details and analytical data for compounds **4**−**6**, **10**−**14**, **26**, **29**−**31**, **33**, and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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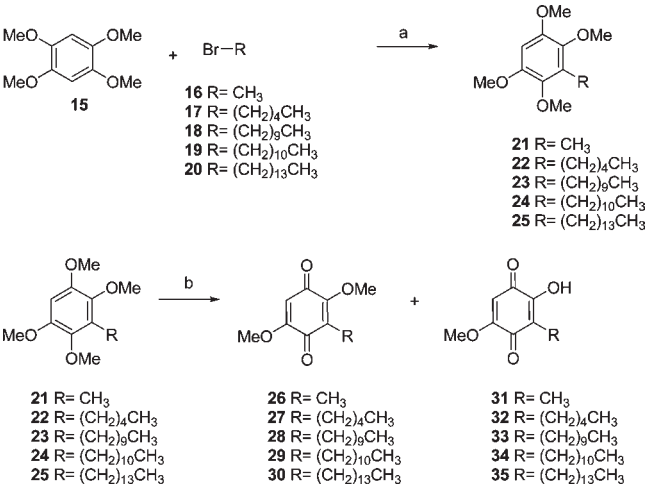
Scheme 4 [a]



[a] Reagents and conditions: (a) *n*BuLi, HMPA, THF, −40 °C→ room temperature, 12 h; (b) CAN, CH_3CN, 1 h, −7 °C → room temperature.

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