New Chlorinated Diphenyl Ethers from an *Aspergillus* Species

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Two new chlorinated diphenyl ethers (**5**, **6**) have been isolated from the culture broth of an *Aspergillus* species obtained from leaf litter, together with the known benzophenone sulochrin (**1**), the grisandiene geodin (**2**), and the diphenyl ether asterric acid (**3**). The structure of another metabolite, methyl asterrate (**4**), was confirmed by single-crystal X-ray structure analysis.

As part of an investigation of coprophilous and folicolous fungi as sources of bioactive compounds, we have investigated the metabolites produced by an *Aspergillus* sp. recovered from leaf litter. In preliminary bioassays, the fungus showed significant in vitro lignolytic activity, and it antagonized the growth of the phytopathogenic fungus *Rhizoctonia solani*.

Results and Discussion

The fungus, grown in potato dextrose broth medium for 4 weeks, produced significant amounts of metabolites that could be obtained by extraction with EtOAc of the culture broth (pH 7), before and after acidification (pH 2), and of the mycelium. Isolation of the individual components afforded the known benzophenone sulochrin (**1**),[1] the grisandiene geodin (**2**),[2] and the diphenyl ether asterric acid (**3**).[3,4] The NMR spectral parameters of **3**, assigned with the aid of HMBC and HMQC techniques, are listed in Table 1. This serves to correct some misassignments[5] and incomplete data[6] in the literature.

A fourth metabolite was tentatively determined to be methyl asterrate (**4**) on the basis of spectral properties. A compound with this structure has been isolated previously from *Oospora sulphure ochrace* and named trimethylosoic acid. [3] Since spectral parameters do not reveal unambiguously the substitution pattern on the phenyl rings, a definitive assignment was sought from single-crystal X-ray diffraction studies that confirmed the structure shown in **4** as described below.

A mono- and a dichloro derivatives of methyl asterrate were also isolated. The structure of the dichloro derivative (HREIMS $C_{18}H_{16}Cl_2O_8$) (**5**) was readily determined from the ^{1}H NMR spectrum. The *meta*-coupled protons on the A-ring in methyl asterrate (**4**) can be distinguished from those on ring-B by the long-range coupling ($J = 0.5$ Hz) of the former with the aromatic methyl (δ_H 2.24). In the dichloro derivative (**5**) the signals for these two protons were absent and the signal for the aromatic methyl appeared as a singlet (δ_H 2.49). The location of the chlorine in the monochloro derivative (**6**) could be inferred from the shielding effect observed for the C-1 carbon (δ_C 162.6) compared to the chemical shift (δ_C 164.0) for the same carbon in methyl asterrate (**4**) (Table 1). This is consistent with the shielding effect of a *p*-chlorine, suggesting that the chlorine atom is located at C-4′. A search of the literature revealed that a compound with identical structure had been prepared from the corresponding naturally occurring A-ring acid (**7**), a metabolite produced by a *Penicillium* sp.[7] Although the melting point was not quoted, the ^{1}H NMR was identical to that obtained for **6**. Interestingly, the C-6′ chloro regioisomer of **7** was found to cooccur with **7** in *Penicillium citrinum*.[8]

Table 1. ^{13}C NMR Data for Compounds **3**−**6** (125 MHz, δ ppm)

carbon	**3**[a]	**3**[b]	**4**[c]	**5**[c]	**6**[a]	**6**[c,d]
1	137.2	134.6	136.6	139.2	136.0	136.3
2	126.4	125.6	125.7	123.1	127.0	125.7
3	109.0	109.3	108.4	108.4	109.0	108.4
4	156.6	156.9	153.9	151.2	156.8	153.4*
5	106.7	105.6	105.8	105.0	105.8	104.5
6	154.7	154.8	153.3	152.4	155.6	153.8*
7	56.7	56.7	56.4	56.5	56.6	56.4
8	168.6	165.6	165.8	166.5	167.5	165.5
9	53.4	52.7	52.5	53.0	52.7	52.9
1′	164.0	164.3	163.0	155.4	162.6	158.4*
2′	106.7	100.5	100.7	106.5	104.8	101.9
3′	161.3	159.4	159.8	150.9	160.9	157.8*
4′	106.3	106.0	104.9	118.3	107.9	106.6
5′	144.3	147.8	146.1	141.4	143.7	143.6
6′	112.1	112.6	111.1	117.8	115.2	114.7
7′	21.8	22.0	22.1	18.7	21.0	21.1
8′	175.9	171.7	171.7	170.0	172.1	171.5
9′			52.4	52.4	52.6	52.4

[a] Spectra recorded in d_4-MeOH. [b] Spectra recorded in d_6-acetone. [c] Spectrum recorded in $CDCl_3$. [d] Values marked with an asterisk can be interchanged.

Chlorinated diphenyl ethers are common constituents of lichens and marine sponges, but are relatively rare as fungal metabolites. In fungi, two main types are observed. Chlorination in the A-ring is found in metabolites from *Penicillium* and *Aspergillus* spp., whereas B-ring chlorination occurs in metabolites from *Xylaria*[9] and *Pestalotiopsis* spp.[10] The biosynthesis of these compounds is generally considered to proceed from the anthraquinone emodin, via sulochrin, and the grisandienes such as geodin (Figure 1).[11,12] Given the isolation of compounds **5** and **6**, the pathway allows for the formation of mono- or dichlorinated analogues from sulochrin (**1**) and for an extra methylation step involving the newly formed carboxylic acid in asterric acid (C8) or its chloro derivatives.

Considerable interest has been shown in the biological activity of asterric acid and its chlorinated metabolites. Asterric acid (**3**) was the first non-peptide endothelin (ET) binding inhibitor discovered.[5] It specifically inhibited (IC_{50} 10^{-5} M) binding of ET-1 to the ET_A receptor of A10 cells.

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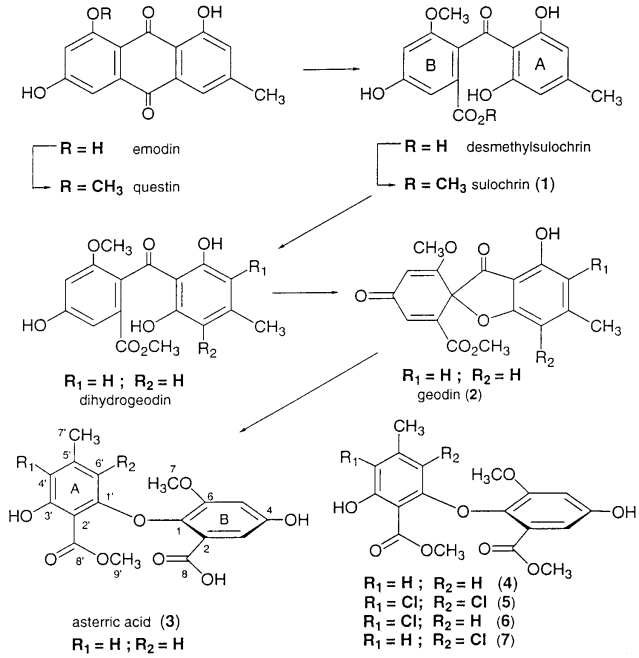
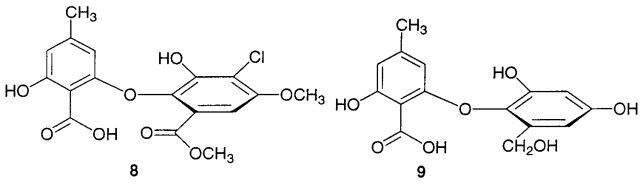


Figure 1. Biosynthetic relationship between anthraquinones, benzophenones, grisanes, and diphenyl ethers.

ET-1 exhibits potent and long-lasting vasoconstrictive activity. A number of derivatives of asterric acid have been claimed to be useful in the treatment of myocardial infarction and renal insufficiency.[7] The chlorinated derivatives of **3** have phosphodiesterase inhibitory activity[8] and inhibit the formation of melanins in cultured human melanocytes.[13]

Compounds **1**−**6** did not show activity toward *E. coli* or the phytopathogenic fungi *Gaeumannomyces graminis* var *tritici* and *Rhizoctonia solani*, at concentrations lower than 200 ppm. The antinematodal activity was tested in a bioassay using the model nematode *Caenorhabditis elegans*.[14] Moderate activity was observed for **1**−**3** (LD_{90} 50 ppm) and **4** and **5** (LD_{90} 75 ppm) over 16−24 h, whereas **6** (LD_{50} 100 ppm) was less active. The ability of these compounds to inhibit germination was tested using cress seeds.[15] The monochloro derivative (**6**) was active at 10 ppm, the dichloro derivative (**5**) at 12 ppm, whereas **1**−**3** inhibited germination only at 100 ppm.

Single-crystal X-ray structure analysis established unambiguously the structure of methyl asterrate (**4**). Views of the solid-state conformation of **4** (Figure 2) and crystal packing (Figure 3) (Supporting Information) are presented. Similar studies have been carried out on the related compounds dihydromaldoxin (**8**)[9] and barceloneic acid (**9**),[16]



and relevant similarities and differences are presented in the sequel. The results of the "low"-temperature single-crystal X-ray structure determination carried out on compound **4** are consistent with the stoichiometry as assigned above; one molecule comprises the asymmetric unit of the structure, bond lengths and angles being generally as expected, inclusive of hydrogen atoms, which were resolved

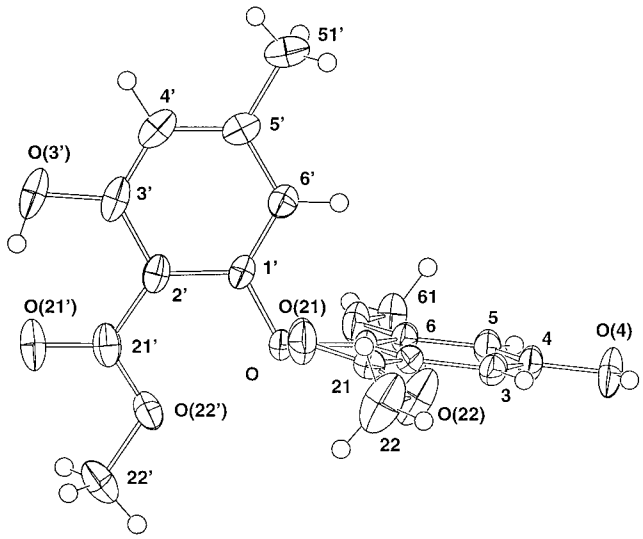


Figure 2. Projection of molecule 1 of **4** (molecule 2 is similar), normal to one of the aromatic planes.

and refined in (x, y, z, U_{iso})$_H$. In **4**, two independent molecules of similar aspect (Figure 2) comprise the asymmetric unit of a centrosymmetric, i.e., achiral, structure. The broad geometry (Table 2, Supporting Information) conforms to that observed in dihydromaldoxin (**8**),[9] in the phenyl rings of which a pair of carbo substituents are also found *ortho* to the pendant ether oxygens. In dihydromaldoxin, the C_6/C_6 interplanar dihedral angle is 86.8(1)°, the C_2O_2/C_6 interplanar dihedrals being 9.7(1)°, 0.9(2)°; in barceloneic acid (**9**),[16] where one of the carboxyl groups is supplanted by a hydroxymethylene moiety, the respective angles are 84.1(2)°, 3.6(2)°. The dihedral angles between the two (C_6) aromatic ring planes of the two molecules of **4** are 88.87(9)°, 78.07(9)°; that is, they lie mutually quasi-normal. The substitution patterns of the two halves of the molecules differ, with concomitant differences in geometry most pronounced among the angles (Table 2). In both halves, there is an OCOMe substituent at the *2*-position of the aromatic ring, but, although essentially coplanar in both situations, the disposition differs, presumably correlating with the presence or absence of a neighboring substituent at the 3-position. In the primed half, the phenolic hydrogen hydrogen-bonds intramolecularly to the C═O oxygen O(21′), which lies directed toward it, also true of dihydromaldoxin (**8**) and barceloneic acid (**9**); in the other half, the OCOMe moiety is rotated through 180°, so that O(21) now lies adjacent to the central oxygen, also true of dihydromaldoxin. Concomitantly, we find changes in the exocyclic angles at 1/1′, 2/2′, with changes in the bond lengths to the pendants at those atoms, the latter perhaps also affected by electronic effects of the substituents at C(3$^{(\prime)}$−6$^{(\prime)}$); angular variations are also found between the OCOMe pendants themselves, while the O···O(2x$^{(\prime)}$) distances also differ, all those effects presumably concerted. In the unprimed sections, the phenolic moiety is found at C(4), hydrogen bonds necessarily exocyclic and differing in the associated hydrogen orientations, that in molecule 1 "*cis*" to the carboxymethyl group, while in molecule 2 it is "*trans*", with concomitant differences in the exocyclic angles. In both molecules the associated hydrogen bonds are intermolecular. The crystal packing (Figure 3) is of interest, the unprimed planes of molecules 1 lying quasi-normal to *a*, while in molecule 2 it is the primed planes which are disposed thus, the other planes interleaved in a stack normal to *c*.

Experimental Section

General Experimental Procedures. Melting points were determined using a Kofler apparatus and are uncorrected. Other general procedures have been described.[17]

Organism and Fermentation. A strain of an unidentified *Aspergillus* sp. (deposited with the Soil Science and Plant Nutrition Group, Faculty of Agriculture; Registry Number 8143) was recovered from leaf litter near Perth, Western Australia. Single spore isolates were obtained by growing the strain on potato dextrose agar (PDA). Spore suspensions were spread on 2% water agar plates and were incubated at 25 °C for 24 h. Isolated germinating spores were selected using a compound microscope and were transferred onto fresh PDA plates to obtain pure cultures. Potato dextrose broth (2 L) was inoculated with spores of the fungus and left standing at 25 °C for 4 weeks.

Extraction and Isolation. The culture medium (pH ~7) was separated from the mycelium by filtration and extracted with EtOAc (3 × 350 mL). The concentrated extract (468.1 mg) was subjected to chromatography (Si gel) using a Chromatotron. Elution with stepwise gradient from diisopropyl ether−hexane (2:1) to MeOH afforded 18 fractions. Fractions 1−5 (37.1 mg) were rechromatographed (gradient, diisopropyl ether to diisopropyl ether−$CHCl_3$, 2:1) to yield **6** (5.9 mg), asterric acid methyl ester (**4**) (6.6 mg), and geodin (**2**) (7.9 mg). Fractions 6−8 were similarly treated and provided further quantities of **4** (23.3 mg), **2** (3.8 mg), and methyl dichloro asterrate (**5**) (20.7 mg). Repeated chromatography of fractions 9−13 (49.4 mg) (diisopropyl ether to 10% MeOH) yielded a further quantity of **5** (14.1 mg) and an unidentified compound (6.1 mg). Fractions 14−18 were rechromatographed ($CHCl_3$ to $CHCl_3$−MeOH, 4:1) to afford **3** (17.9 mg) and sulochrin (**1**) (12.1 mg). The total amounts of metabolites obtained were **1** (12.1 mg), **2** (11.7 mg), **3** (17.9 mg), **4** (29.9 mg), **5** (26.4 mg), and **6** (5.9 mg). Acidification (pH 2) of the culture filtrate and extraction with EtOAc yielded a further quantity (560 mg) of extract. Chromatography as above afforded **3** (68.5 mg) and sulochrin (**1**) (20 mg) and a mixture of acids. Extraction of the mycelium with methanol yielded an extract (160 mg) from which quantities of **4** (40 mg), fatty acids (16 mg), and glucose (42 mg) could be recovered on chromatographic separation.

Sulochrin (1): prisms from acetone/$CHCl_3$, mp 231−234 °C (lit.[1] 240−245 °C); ^{1}H NMR (500 MHz; d_6-acetone) δ 10.82 (1H, br s, OH); 8.79 (1H, br s, OH), 7.10 (1H, d, J = 2.0 Hz, H-5); 6.71 (1H, d, J = 2.0 Hz, H-3); 6.16 (2H, q, J = 0.6 Hz, H-3′, 5′), 3.68, 3.64 (each 3H, s, H_3-7, −8), 2.17 (3H, s, H_3-7′); ^{13}C NMR (125 MHz; d_6-acetone) δ 200.6 (s), 166.6 (s). 162.8 (s), 158.9 (2s), 158.2 (s), 148.2 (s), 129.5 (s), 128.0 (d), 110.5 (s), 108.7 (2d), 108.4 (d), 104.0 (d), 56.3 (q), 52.2 (q), 21.9 (q); EIMS m/z 332, [M^+] (67%) ($C_{17}H_{16}O_7$) 301 (70), 300 (81), 272 (54), 269 (100) 209 (50), 151 (47).

Geodin (2): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.43 (1H, br s, OH); 7.15 (1H, d, J = 1.5 Hz, H-3); 5.83 (1H, d, J = 1.5 Hz, H-5); 3.75, 3.71 (each 3H, s, H_3-7, -8), 2.57 (3H, s, H_3-7′); in good agreement with the values quoted in the literature;[11] ^{13}C NMR δ 193.3 (s), 185.0 (s). 167.9 (s), 165.4 (s), 163.4 (s), 149.3 (s), 146.6 (s), 137.5 (d), 137.0 (s), 114.7 (s), 109.4 (s), 108.8 (s), 104.4 (d), 84.5 (s), 57.0 (q), 53.1 (q), 18.7 (q); EIMS m/z 402, 400, 398 [M^+] (17, 74, 100%) ($C_{17}H_{12}Cl_2O_7$) 343, 341, 339 (9, 37, 57), 178, 176, 174 (4, 15, 22).

Asterric acid (3): needles from acetone−$CHCl_3$, mp 193−196 °C (lit.[4] 209−210 °C); ^{1}H NMR (500 MHz; d_6-acetone) δ 11.96, 11.32 9.06 (each s, OH); 7.04 (1H, d, J = 2.8 Hz, H-3); 6.92 (1H, d, J = 2.8 Hz, H-5); 6.47 (1H, dq, J = 1.5, 0.6, H-6′); 5.91 (1H, dq, J = 1.5, 0.6, H-6′, H-4′); 3.81, 3.73 (each 3H, s, H_3-7, -9′), 2.16 (3H, t, J = 0.5 Hz, H_3-7′); ^{13}C NMR data (Table 1) assigned with the aid of HMQC and HMBC; EIMS m/z 348 [M^+] (58%) ($C_{17}H_{16}O_8$), 330 (70), 271 (51), 167 (100).

Methyl asterrate (4): prisms from EtOAc−hexane, mp 176−180 °C (lit.[3] 185−186 °C); ^{1}H NMR (500 MHz; $CDCl_3$) δ 11.57, 11.56 (each s, OH); 6.94 (1H, d, J = 2.8 Hz, H-3); 6.68 (1H, d, J = 2.8 Hz, H-5); 6.43 (1H, m, H-6′); 5.75 (1H, m, H-4′); 3.94, 3.75, 3.68 (each 3H, s, H_3-7, -9, -9′), 2.24 (3H, t, J = 0.5 Hz, H_3-7′); ^{13}C NMR data (Table 1); EIMS m/z 362 [M^+] (73%) ($C_{18}H_{18}O_8$), 331 (25), 330 (100), 271 (72), 257 (37).

Methyl dichloroasterrate (5): prisms from $CHCl_3$, mp 144−147 °C; ^{1}H NMR (500 MHz; $CDCl_3$): δ 11.42 (s, OH); 6.86 (1H, d, J = 2.9 Hz, H-3); 6.56 (1H, d, J = 2.9 Hz, H-5); 3.81, 3.74, 3.53 (each 3H, s, H_3-7, -9, -9′), 2.49 (3H, s, H_3-7′); ^{13}C NMR data (Table 1); EIMS m/z 434, 432, 430 [M^+] (12, 51, 75), 402, 400, 398 (14, 71, 100), 343, 341, 339 (10, 51, 80), 329, 327, 325 (11, 54, 80); HRMS m/z 430.021192 ($C_{18}H_{16}{}^{35}Cl_2O_8$ requires 430.022223); 432.017990 ($C_{18}H_{16}{}^{35}Cl^{37}ClO_8$ requires 432.019273).

Methyl chloroasterrate (6): leaflets from EtOAc−hexane, mp 171−174 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 12.26 (1H, OH); 6.97 (1H, d, J = 2.9 Hz, H-3); 6.72 (1H, d, J = 2.9 Hz, H-5); 5.87 (1H, q, J = 0.5 Hz, H-4′); 3.96, 3.75, 3.71 (each 3H, s, H_3-7, -9, -9′), 2.24 (3H, d, J = 0.5 Hz, H3-7′); ^{1}H NMR (500 MHz; CD_3OD) δ 6.84 (1H, d, J = 2.8 Hz, H-3); 6.73 (1H, d, J = 2.8 Hz, H-5); 5.92 (1H, q, J = 0.3 Hz, H-4′); 3.73, 3.67, 3.65 (each 3H, s, H_3-7, -9, -9′), 2.19 (3H, d, J = 0.5 Hz, H_3-7′); ^{13}C NMR data (Table 1) assigned with the aid of HMQC and HMBC; EIMS m/z 398, 396 [M^+] (17, 39) ($C_{18}H_{17}ClO_8$), 366, 364 (41, 100), 307, 305 (23, 60), 293, 291 (16, 43); FABMS 399, 397.

Structure Determination of 4: $C_{18}H_{18}O_8$, M = 362.3; triclinic, space group $P\bar{1}$ (C_i^1, No. 2), a = 8.901(1) Å, b = 13.887(2) Å, c = 14.611(2) Å, α = 109.845(2)°, β = 92.883(2)°, γ = 90.286(2)°, V = 1696 Å^3, D_c (Z = 4) = 1.41$_9$ g cm^{-3}, μ_{Mo} 1.1 cm^{-1}; specimen 0.21 × 0.17 × 0.15 mm. Full sphere of CCD area-detector diffractometer data were measured at ca. 153 K (Bruker AXS instrument; $2\theta_{max}$ = 58°; ω-scans; monochromatic Mo Kα radiation, λ = 0.7107$_3$ Å), yielding 19 060 reflections, merging to 8208 independent (R_{int} = 0.019), 6297 with $F > 4\sigma(F)$ being used in the full matrix least squares refinement, refining anisotropic thermal parameter forms for C, O, (x, y, z, U_{iso})$_H$ also being refined. Conventional residuals R, R_w (weights ($\sigma^2(F) + 0.0004F^2$)$^{-1}$) on $|F|$ were 0.061, 0.070. Neutral atom complex scattering factors were employed within the context of the Xtal 3.7 program system.[18] Pertinent results are given above and in the figures, the latter showing 50% amplitude displacement ellipsoids for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å.[19]

Bioassays. To evaluate ligninase production, agar plugs of the fungus from growing margins of colonies on PDA were inoculated on agar containing 0.02% polymeric dye R-478 (Sigma, MO). The production of appropriate enzyme activity was indicated by a clear zone in the agar under and/or around the fungal colony. Antifungal activity was tested using the dialysis membrane overlay technique.[20] Previously described methods were used to test for antinematodal activity[14] and for inhibition of cress seed germination.[15]

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Supporting Information Available: Molecular non-hydrogen geometries for **4** (Table 2) and projection of unit cell contents (Figure 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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