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METABOLITES OF *PENIOPHORA POLYGONIA*, PART 2.[1] SOME AROMATIC COMPOUNDS

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ABSTRACT.—Three new benzaldehyde derivatives **3**, **4**, and peniophoral [**5**], and the *erythro*-diol **8** have been isolated from the culture broth of the fungus *Peniophora polygonia*, in addition to the known aromatic compounds **1**, **2**, and **7** and several drimane sesquiterpene lactones. The absolute configurations of **5** and **8** were deduced from consideration of asymmetry models and from cd spectra.

Recently we reported the isolation and characterization of several drimane sesquiterpene lactones from liquid cultures of *Peniophora polygonia* (Pers.: Fr.) Bourd. & Galzin (=*Corticium polygonium*) (Corticiaceae), a fungus associated with decay of aspen which has been shown to be antagonistic to *Phellinus tremulae*, another decay-causing fungus in aspen (1). In addition to these sesquiterpenes, several aromatic compounds were isolated after extraction of the filtered culture broth with Et_2O. We describe herein the purification and structure elucidation of these compounds.

RESULTS AND DISCUSSION

Pe. polygonia was cultured (23°, 24 days) on a medium of 10% V-8 juice containing 1% added glucose. The culture broth was filtered, and the filtrate was extracted with Et_2O. The crude extract was subjected to flash chromatography, and the fractions obtained were further purified by preparative tlc.

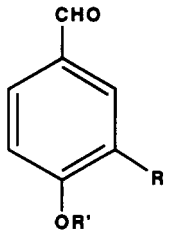
p-Hydroxybenzaldehyde [**1**] and three derivatives thereof, including its *O*-isoprenyl derivative **2** which has been prepared previously by synthesis (2), were obtained. *p*-Hydroxybenzaldehyde is a known fungal metabolite (3), but **2** has not been reported as a natural product.

3-Hydroxy-4-(3-methyl-2-butenyl)oxybenzaldehyde [**3**] was isolated as an oil that solidified at −20°. Its spectroscopic properties are similar to those of **2**, except for the presence of an hydroxyl group in the meta position. The location of the isoprenyloxy group in the para position is based on the nOe enhancement of the signal of H-5 on irradiation of H-1′.

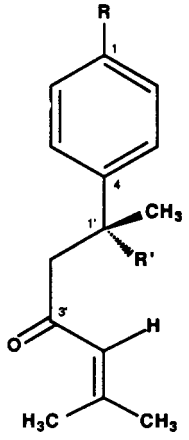
Compound **4** displayed aromatic ^1H- and ^{13}C-nmr signals almost identical with those of compound **2**, except that one of the methyl signals was replaced by a two-proton singlet at 4.24 ppm in the ^1H-nmr spectrum. The *Z* configuration of the double bond was demonstrated by the nOe spectrum: on irradiation of the Me hydrogens, an enhancement of the olefinic proton signal (H-2′), but not of H-1′, was observed. This configuration accounted for the relatively high-field chemical shift of CH_2OH (at 62.1 ppm) in the ^{13}C-nmr spectrum, due to the shielding effect of C-1′ (4).

Compound **5**, which we named peniophoral, was obtained as a colorless oil, $[\alpha]_D$ +32.6°. The molecular formula $C_{15}H_{18}O_3$ was based on cims (NH_3, 100% $[M+1]^+$) and hreims ($[M-Me]^+$ and $[M-H_2O]^+$ as highest peaks). It showed hydroxyl (3550–3200 cm^{-1}) and two carbonyl (1701 and 1678 cm^{-1}) absorptions in the ir spectrum and uv absorbance (MeOH) at 252 nm (15,000). In the nmr spectra it showed the characteristics of a para-substituted benzaldehyde: a singlet at 9.99 ppm (CHO) and two two-proton doublets (at 7.61 and 7.84 ppm, $J=7.8$ Hz) in the ^1H-

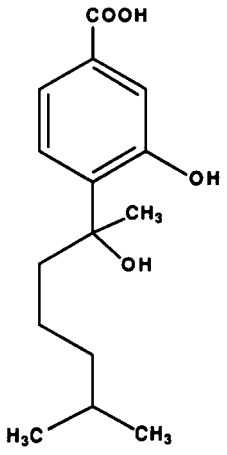
[1]For part 1, see Ayer and Trifonov (1).



1 R=H, R'=H
2 R=H, R'=$CH_2CH=C(Me)_2$
3 R=OH, R'=$CH_2CH=C(Me)_2$
4 R=H, R'=$CH_2CH=C(Me)CH_2OH$



5 R=CHO, R'=OH
6 R=Me, R'=H



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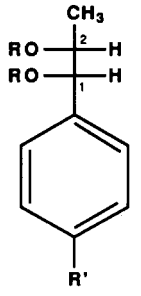

8 R=H, R'=H
9 R=H, R'=$OCH_2CH=C(Me)_2$
10 R=PhCO, R'=H
11 R=PhCO, R'=$OCH_2CH=C(Me)_2$

nmr spectrum, and one doublet at 192.0 ppm (CHO), two singlets (at 135.0 and 159.0 ppm), and two doublets (at 125.5 and 129.9 ppm) in the ^{13}C-nmr spectrum. The presence of three methyl groups was deduced from the ^{1}H-nmr (s at 1.52 ppm and doublets at 1.87 and 2.06 ppm with J = ca. 1 Hz) and the ^{13}C-nmr spectrum (q at 21.1, 27.9, and 30.7 ppm). The signals in the ^{13}C-nmr spectrum at 201.2 (s), 124.0 (d), and 154.9 (s) ppm clearly indicated the presence of a $COCH=C(CH_3)_2$ unit (5,6). The presence of a CH_2 group with diastereotopic protons (d at 2.88 ppm and d at 3.16 ppm, J = 17.3 ppm) as demonstrated by the ^{1}H-nmr spectrum, and the optical activity of peniophoral, indicated that the remaining OH and Me groups are linked to a chiral carbon atom which is also attached to the para-substituted benzaldehyde moiety and to the CH_2 group, as shown in structure **5**. This structure accounts for the facile loss of Me, H_2O, and C_6H_9O in the hreims spectrum. The absolute configuration of peniophoral [**5**] was deduced to be *R* from the positive optical rotation and consideration of Brewster's asymmetry rules (7).

A similar compound, (+)-ar-turmerone [**6**] has been previously isolated from rhizomes of *Curcuma longa* L., and its absolute configuration was established to be *S* (8).

A related optically inactive metabolite named sydonic acid [**7**] has been isolated from the mold *Aspergillus sydowi* (9).

Erythro-1-phenylpropane-1,2-diol [**8**] and a *p*-isoprenyloxy derivative **9** were obtained as colorless oils. The spectroscopic data for **8**, including the optical rotation, were identical with those reported in the literature (10). The diol **9** showed the molecular formula $C_{14}H_{20}O_3$ (hreims). The similarity between the propane-1,2-diol substructure of **8** and that of **9**, in particular the characteristic two aromatic doublets in the ^{1}H-nmr spectrum, suggested the structure of a *p*-substituted derivative of **8**. The small vicinal coupling constant $^3J_{H1,H2}$ (4.6 Hz) was indicative of an erythro diol. The presence of an isoprenyloxy group at the para position was deduced from the similarity between the ^{1}H- and ^{13}C-nmr signals of **9** and *p*-isoprenyloxybenzaldehyde [**2**]. The absolute configuration of **9** was assigned as 1*S*,2*R* because of the similarity between the cd spectra of **10** and **11** (see Experimental) and by application of Freudenberg's optical shift rule: $\Delta[M]_D$ +230.2° (**8**→**10**), $\Delta[M]_D$ +168.0° (**9**→**11**) (11).

Preliminary bioassays show that the *p*-substituted benzaldehydes **2** and **3** have antifungal activity against *Ph. tremulae*.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Experimental procedures and instrumentation employed are described in Part 1 (1).

ISOLATION OF METABOLITES.—Cultures of *Pe. polygonia* (strain NOF 1494; UAMH 7006) were obtained from Dr. Y. Hiratsuka, Forestry Canada, Northern Forestry Centre, Edmonton. Twelve 2-liter Erlenmeyer flasks, each containing 1 liter of filtered V-8 juice (Campbell Soup Company Ltd.) liquid medium (10 g of glucose, 100 ml of V-8 juice filtered through Celite, and 900 ml of distilled H_2O), were inoculated with ca. 10 ml of a mycelial suspension of *Pe. polygonia* and shaken for 24 days at 23°. The culture broth was filtered through cheesecloth, and the filtrate was extracted with Et_2O (2 × 2 liters). The Et_2O extract was dried over $MgSO_4$ and the solvent removed to afford a crude extract as a pungent yellowish-brown oil. This oil was subjected to flash chromatography on Si gel using gradient elution: petroleum ether-EtOAc (91:9) (400 ml), (83:17) (400 ml), (75:25) (250 ml), and (50:50) (200 ml), and CH_2Cl_2-MeOH (91:9) (200 ml) with fractions of 15 ml being collected. Fraction 8–18 (14 mg) contained pure **2**. Fraction 21–28 (13 mg) contained cinnamolide and *cis*-dihydroconfertifolin (1).

Fraction 33–46 (18 mg) was subjected to preparative tlc with petroleum ether-EtOAc (83:17) (twofold development). The uv-active zone at R_f 0.50 gave pure **3** (14 mg). The uv-active fraction of R_f 0.30 gave a crude product which was crystallized from petroleum ether to afford pure **1** (1.1 mg).

Fraction 48–57 (16 mg) was crystallized from petroleum ether to give peniopholide (6 mg) (1). The mother liquor was subjected to preparative tlc with toluene-EtOAc-MeOH (93:5:2) (fourfold development). The uv-active zone at R_f 0.4 was eluted with $CHCl_3$ to afford **5** (1.5 mg).

Fractions 58–70 (6 mg) and 71–83 (8 mg) gave 6β-hydroxycinnamolide and 6α-hydroxycinnamolide, respectively, after crystallization from petroleum ether (1).

Fraction 84–86 (3 mg) contained 7α-hydroxyconfertifolin as the main component (1).

Fraction 87–89 (10 mg) was purified by preparative tlc with petroleum ether-EtOAc-CH_2Cl_2-MeOH (63:16:16:5) (three-fold development). The uv-active zone at R_f 0.45 afforded pure **8** (6 mg). The uv-active material at R_f 0.52 was eluted with CH_2Cl_2-MeOH (90:10), and the crude product was further purified by preparative tlc with petroleum ether-toluene-EtOAc-CH_2Cl_2-MeOH-HOAc (46:14:25:12:2:1) (three-fold development) to give pure **4** (1.4 mg).

Fraction 90–91 (10 mg) was subjected to preparative tlc with petroleum ether-EtOAc (2:1) (threefold development). The uv-active zone at R_f 0.50 gave **9** (3.5 mg).

4-Hydroxy-benzaldehyde [**1**].—Identical (mp, tlc, ir, eims) with an authentic sample.

4-(3-Methyl-2-butenyl)oxybenzaldehyde [**2**].—Oil: ir ν max ($CHCl_3$) cm^{-1} 2980, 2932, 2920, 2870, 1692, 1601; hreims *m/z* $[M]^+$ 190.0987 (3) ($C_{12}H_{14}O_2$ requires 190.0994), $[M-C_5H_9]^+$ 121 (50), $[M-C_5H_9O]^+$ 105 (4), $[C_5H_9O]^+$ 85 (20), $[C_5H_9]^+$ 69 (100); ^{1}H nmr (360 MHz, $CDCl_3$) 1.76 (3H, s, *Z*-Me), 1.81 (3H, s, *E*-Me), 4.60 (2H, d, J = 6.8, CH_2O), 5.49 (1H, br t, J = 6.8, H-2′), 7.00 (2H, d, J = 8.8, H-3, H-5), 7.82 (2H, d, J = 8.8, H-2, H-6), 9.88 (1H, s, CHO).

3-Hydroxy-4-(3-methyl-2-butenyl)oxybenzaldehyde [**3**].—Mp 60.0–65.0°; ir ν max ($CHCl_3$) cm^{-1} 3550–3100 br, 2970, 2930, 2910, 2870, 1683; uv λ max (MeOH, ε) 224 (55,200), 230 (55,400), 268 (36,800), 300 (21,000), 307 (20,300); hreims *m/z* $[M]^+$ 206.0940 (27) ($C_{12}H_{14}O_3$ requires 206.0943),

138 (54), 137 (22), 69 (100); ^{1}H nmr (400 MHz, $CDCl_3$) 1.71 (3H, br s, *Z*-Me), 1.78 (3H, d, J = 1.5, *E*-Me), 4.66 (2H, d, J = 6.8, H-1′), 5.48 (1H, t × hept, J = 6.8, 1.3, H-2′), 5.84 (1H, s, OH), 6.96 (1H, d, J = 8.0, H-5), 7.40 (1H, dd, J = 8.0, 2.0, H-6), 7.43 (1H, d, J = 2.0, H-2), 9.83 (1H, s, CHO); irradiation at 4.66 ppm (H-1′) gave a 9% nOe of the H-5 doublet (at 6.96 ppm); ^{13}C nmr (100 MHz, $CDCl_3$) 18.2 (Me-*Z*), 25.7 (Me-*E*), 66.0 (C-1′), 111.3 (C-5), 114.1 (C-2′), 118.4 (C-2), 124.3 (C-6), 130.6 (C-1), 139.9 (C-3′), 146.4 (C-4), 151.2 (C-3), 190.9 (CHO).

4-{(Z)-(4-Hydroxy-3-methyl-2-butenyl)oxy}benzaldehyde [**4**].—Oil: ir ν max (CH_2Cl_2) cm^{-1} 3550–3250 br, 2930, 2870, 1685, 1600; hreims *m/z* [M]$^+$ 206.0939 (2) ($C_{12}H_{14}O_3$ requires 206.0943), 123 (38), $[HOC_6H_4CHO]^+$ 122 (100), $[OC_6H_4CHO]^+$ 121 (91), 93 (8), 84 (12), $[C_5H_9O]^+$ 69 (10), 65 (10), $[C_4H_7O]^+$ 55 (10); ^{1}H nmr (360 MHz, $CDCl_3$) 1.90 (3H, d, J = 1.1, Me), 4.24 (2H, s, H-4′), 4.69 (2H, d, J = 6.8, H-1′), 5.65 (1H, br t, J = 6.8, H-2′), 7.00 (2H, d, J = 8.7, H-3, H-5), 7.83 (2H, d, J = 8.7, H-2, H-6), 9.89 (1H, s, CHO). Irradiation at 5.65 gave 4.69 (s), 1.90 (s). ^{13}C nmr (125 MHz, $CDCl_3$) 21.6 (Me), 62.1 (C-4′), 64.3 (C-1′), 115.0 (C-3, C-5), 121.8 (C-2′), 130.1 (C-1), 132.1 (C-2, C-6), 141.3 (C-3′), 163.6 (C-4), 190.8 (CHO).

(R)-(+)-4-(1-Hydroxy-1,5-dimethyl-4-hexen-3-onyl)benzaldehyde [**5**].—Oil: $[\alpha]^{21}D$ +32.6° (c = 0.23, MeOH); cd $\Delta\epsilon_{238}$ −ca. 1.3, $\Delta\epsilon_{258}$ +4.5 (c = 0.023, MeOH); ir ν max ($CHCl_3$) cm^{-1} 3550–3200 br, 2977, 2931, 2913, 1701, 1678, 1607; uv λ max (MeOH, ε) 252 (15,000); hreims *m/z* [M − Me]$^+$ 231.1016 (8) ($C_{14}H_{15}O_3$ requires 231.1021), $[M - H_2O]^+$ 228 (7), $[M - COCH{=}C(Me)_2]^+$ 163 (35), $[M - CH_2COCH{=}C(Me)_2]^+$ 149 (20), 133 (17), $[C_6H_4CHO]^+$ 105 (56), $[CH_2COCH{=}C(Me)_2]^+$ 98 (24), $[COCH{=}C(Me)_2]^+$ 83 (100), 55 (21); cims (NH_3) $[M + 1 + NH_3]^+$ 264 (14), $[M + 1]^+$ 247 (100), 229 (16), 146 (38), 117 (16), 116 (12), 100 (47), 99 (28), 83 (75), 82 (53); ^{1}H nmr (360 MHz, $CDCl_3$) 1.52 (3H, s, 1′-Me), 1.55 (1H, s, OH), 1.87 (3H, s, J = 1.1, *E*-Me), 2.06 (3H, d, J = 0.9, *Z*-Me), 2.88 (1H, d, J = 17.3, H-2′), 3.16 (1H, d, J = 17.3, H-2′), 5.99 (1H, br s, H-4′), 7.61 (2H, d, J = 7.8, H-3, H-5), 7.84 (2H, d, J = 7.8, H-2, H-6), 9.99 (1H, s, CHO); ^{13}C nmr (125 MHz, $CDCl_3$) 21.1 (*Z*-Me), 27.9 (*E*-Me), 30.7 (CH_3-1′), 53.6 (C-2′), 73.8 (C-1′), 124.0 (C-4′), 125.3 (C-3, C-5), 129.9 (C-2, C-6), 135.0 (C-1), 154.9 (C-5′), 159.0 (C-4), 192.0 (CHO), 201.2 (C-3′).

(1S,2R)-(−)-1-Phenylpropane-1,2-diol [**8**].—Oil: $[\alpha]^{21}D$ −17.4° (c = 0.86, EtOH); [lit. (10) $[\alpha]^{21}D$ −18.2°, c = 7, EtOH]; ir ν ($CHCl_3$) cm^{-1} 3400–3100 br, 3062, 3029, 2976, 2931, 2911, 2880, 1605; hreims *m/z* [M]$^+$ 152.0828 (0.4) ($C_9H_{12}O_2$ requires 152.0838), 123 (14), 108 (100), 107 (81), 79 (89), 77 (39); ^{1}H nmr (360 MHz, $CDCl_3$) 1.10 (3H, d, J = 6.4, Me), 2.05 (2H, br s, 2 OH), 4.02 (1H, qd, J = 6.4, 4.4, H-2), 4.69 (1H, d, J = 4.4, H-1), 7.28–7.38 (5H, m, C_6H_5); ^{13}C nmr (90 MHz, $CDCl_3$) 17.3 (C-3), 71.3 (C-2), 77.5 (C-1), 126.6, 127.9, 128.4 (CH arom.), 140.3 (C arom.).

(1S,2R)-(−)-1-{4-(3-Methyl-2-butenyl)oxyphenyl}propane-1,2-diol [**9**].—Oil: $[\alpha]^{21}D$ −18.3° (c = 0.24, EtOH); ir ν max ($CHCl_3$) cm^{-1} 3600–3100 br, 2976, 2930, 2916, 2880, 1611, 1583, 1511; uv λ max (EtOH, ε) 226 (13,200), 275 (2000), 282 (1800); hreims *m/z* [M]$^+$ 236.1411 (2) ($C_{14}H_{20}O_3$ requires 236.1413), $[M - MeCH(OH)]^+$ 191 (6), $[M - C_5H_8]^+$ 168 (6), 149 (2), $[M - MeCH(OH) - C_5H_9]^+$ 123 (100), 95 (13), 69 (21); ^{1}H nmr (360 MHz, $CDCl_3$) 1.11 (3H, d, J = 6.3, H-3), 1.75 (3H, s, H-4″), 1.80 (3H, s, H-5″), 1.40–2.00 (2H, m, 2 × OH), 3.99 (1H, qd, J = 6.3, 4.6, H-2), 4.51 (2H, d, J = 6.6, CH_2O), 4.59 (1H, d, J = 4.6, H-1), 5.49 (1H, br t, J = 6.6, H-2″), 6.91 (2H, d, J = 8.7, H-3′, H-5′), 7.28 (2H, d, J = 8.7, H-2′, H-6′); ^{13}C nmr (100 MHz, $CDCl_3$) 17.67, 18.2 (C-3, *Z*-Me), 25.8 (*E*-Me), 64.8 (C-1″), 71.2 (C-2), 77.4 (C-1), 114.6 (C-2″), 119.6 (C-3′, C-5′), 127.9 (C-2′, C-6′), 132.3 (C-1′), 138.3 (C-3″), 158.6 (C-4′).

(1S,2R)-(+)-1,2-Dibenzoyloxy-1-phenylpropane [**10**].—A solution of **8** (2.0 mg) and benzoyl chloride (20 mg) in pyridine (30 mg) was kept at room temperature for 24 h; then toluene (0.5 ml) was added and the solvent evaporated. Preparative tlc of the resulting product, eluting with petroleum ether-EtOAc (83:17), afforded **10** as a colorless solid: mp 86.0–91.0° [lit. (10) mp 97°]; $[\alpha]^{21}D$ +56.2° (c = 0.16, EtOH); cd $\Delta\epsilon_{224}$ +9.8, $\Delta\epsilon_{270}$ +ca. 1.1 (c = 0.017, EtOH); ir ν max ($CHCl_3$) cm^{-1} 3060, 3030, 2980, 2930, 1721, 1590; uv λ max (EtOH, ε) 229 (25,400), 273 (1830), 280 (1470); hreims *m/z* [M − PhCOOH]$^+$ 238.0993 (17) ($C_{16}H_{14}O_2$ requires 238.0993), 211 (16), 105 (100); ^{1}H nmr (360 MHz, $CDCl_3$) 1.43 (3H, d, J = 6.6, Me), 5.62 (1H, qd, J = 6.6, 4.1, H-2), 6.29 (1H, d, J = 4.1, H-1), 7.30–7.65 (11H, m, H arom.), 7.97 (2H, dd, J = 8.0, 1.3, PhCO-ortho), 8.11 (2H, dd, J = 8.0, 1.3, PhCO-ortho).

(1S,2R)-(+)-1,2-Dibenzoyloxy-1-{4-(3-methyl-2-butenyl)oxyphenyl}propane [**11**].—Prepared by benzoylation of **9** (2.6 mg) as described above and purified using petroleum ether-EtOAc (90:10). Oil: $[\alpha]^{21}D$ +28.1° (c = 0.26, EtOH); cd $\Delta\epsilon_{233}$ +11.4, $\Delta\epsilon_{265}$ +ca. 1.1 (c = 0.026, EtOH); ir ν max ($CHCl_3$) cm^{-1} 3070, 3040, 2990, 2935, 2860, 1720, 1612, 1602; uv λ max (EtOH, ε) 229 (29,900), 273 (2530), 280 (2030); hreims *m/z* [M]$^+$ 444.1927 (0.3) ($C_{28}H_{28}O_5$ requires 444.1936), 322 (2), 254 (31), 227 (12), 105 (100); ^{1}H nmr (360 MHz, $CDCl_3$) 1.42 (3H, d, J = 6.4, H-3), 1.73 (3H, s, *Z*-Me), 1.79 (3H, s, *E*-Me), 4.49 (2H, d, J = 6.7, H-1″), 5.48 (1H, br t, J = 6.7, H-2″), 5.60 (1H, qd, J = 6.4, 4.2, H-2), 6.21 (1H,

d, $J = 4.2$, H-1), 6.91 (2H, d, $J = 8.7$, H-3′), 7.35–7.60 (8H, m, H arom.), 7.98 (2H, d, $J = 7.8$, PhCO-ortho), 8.09 (2H, d, $J = 7.5$, PhCO-ortho).

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