the values were 5.7 and 8.3% rubber, respectively.

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Chemistry of Toxic Range Plants. Water-Soluble Lignols of Ponderosa Pine Needles

A water-soluble fraction of the acetone extract of Ponderosa pine needles, known to cause abortions in western range cattle, was chromatographically examined. Seven lignol compounds were isolated and characterized, including two monolignols and a dilignol rhamnoside not previously reported to occur naturally. The new compounds are dihydro-*p*-coumaryl alcohol γ-*O*-acetate, dihydroconiferyl alcohol γ-*O*-acetate, and 2,3-dihydro-7-hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)-3-(*O*-rhamnosylmethyl)-5-benzofuranpropanol. Several common flavonoids, organic acids, and pinitol were also isolated.

Ponderosa pine (*Pinus ponderosa*) needles are recognized as a toxic plant material responsible for induced abortion in range cattle consuming the needles in the late fall, winter, and early spring on western range lands (Stevenson et al., 1972). Abortions were observed to begin within 48 h after needle ingestion but may continue as long as 2 weeks after the animals are denied access to the needles. These abortions are characterized by retained placenta and may be accompanied by hemorrhaging. Complications associated with placenta retention may cause animal death.

The abortifacient principle of the pine needles has never been specifically identified. However, in vitro tests of Ponderosa pine needle extractives related to uterine growth and reproductive failure in mice (Chow et al., 1972) have indicated the toxic agent to be water soluble and thermolabile. An examination of the effect of an aqueous extract of fungal-infected Ponderosa pine needles on the uterine growth of mice (Chow et al., 1974) suggested the causative agent to be a fungal metabolite. A more recent study (Anderson and Lozano, 1977) delegated the fungal metabolite to a secondary role while suggesting the toxic constituent affecting reproduction in mice occurs in the pine needle fiber.

The observation of embryonic resorption in mice fed Ponderosa pine needle extracts established the occurrence of a heat-stable toxin soluble in many organic solvents of different polarity (Anderson and Lozano, 1979). Most recently, embryonic resorption has been observed in the uterus of mice administered a mixture of Ponderosa pine needle diterpene resin acids (Kubik and Jackson, 1981). The results of this investigation could not totally account for the earlier observed embryotoxic effects (Anderson and Lozano, 1979) of the Ponderosa pine extracts, but they did suggest that the diterpene resin acids were the principal water-insoluble, heat-stable embryotoxins in the needles. The diterpene resin acids are the first specific pine needle extractive constituents to be biologically evaluated as embryotoxins. The biological evaluation of pine needle toxicity in mammalian systems has thus far been restricted to studies in mice. The results of these studies may bear no relation to the abortion problems observed in ruminants.

The extractive constituents of the needles of some pines have been extensively examined and a large number of diverse chemical constituents have been isolated and characterized, including terpenes (Enzell and Theander, 1962; Norin et al., 1971), carbohydrates (Assarsson and Theander, 1958), aglycons and glycosides of phenylpropanes (Higuchi et al., 1977; Higuchi and Donnelly, 1977, 1978), flavonoids (Higuchi and Donnelly, 1977; Kowalska, 1977), and dilignols (Popoff and Theander, 1975, 1977). This investigation reports the first examination of specific Ponderosa pine water-soluble extractives.

EXPERIMENTAL PROCEDURES

Hammer-milled dry Ponderosa pine needles (5.3 kg), collected near John Day, OR, were sequentually hot solvent

extracted (2-week periods) with petroleum ether (60–80 °C), ethyl ether, acetone, and methanol. Only the acetone extract is described in this investigation.

The concentrated acetone extract (396 g) was mixed with water (1.5 L) and heated (100 °C; steam bath). Celite was added to the slurry, and the mixture was filtered hot through a Celite pad. The aqueous layer was cooled, extracted with ether (3 × 500 mL), and carefully treated with solid $NaHCO_3$ until neutral. The neutralized solution was liquid/liquid extracted (10 days) with ethyl acetate, and the resulting extract was dried (Na_2SO_4) and concentrated, in vacuo to a heavy tar (90 g).

The tarry extract was dissolved in a minimal amount of ethanol and applied to a preparative Sephadex LH-20 column (10 × 100 cm) and gradient eluted with chloroform → chloroform–ethanol (10:1), collecting 500-mL fractions. Each fraction was surveyed by TLC (H_2O saturated butanone; diazotized sulfanilic acid spray), and selected fractions were chosen for preparative rechromatography. Fractions 6, 8, 11, and 12 were rechromatographed on deactivated silica gel (hexane–acetone, 3:2) to obtain enriched fractions of compounds **1**, **2**, **3**, and **4**, respectively. Further chromatography (column and preparative TLC) of the enriched fractions in hexane–acetone and mixtures of chloroform–ethanol yielded chromatographically pure samples of compounds **1** (110 mg) and **2** (90 mg) and purified fractions of **3** (58 mg) and **4** (50 mg). The purified fractions of **3** and **4** were acetylated (Ac_2O/pyridine) and chromatographed (hexane–acetone, 5:1) to yield chromatographically pure acetates of **3** (62 mg) and **4** (54 mg).

Fractions **14**, **16**, and **19** from LH-20 were rechromatographed on LH-20 (H_2O–ethanol, 97:3) to yield enriched fractions of compounds **5**, **6**, and **7**, respectively. Further deactivated silica gel chromatography in mixtures of chloroform–ethanol and chloroform–2-propanol–water yielded chromatographically pure samples of compounds **5** (360 mg), **6** (130 mg), and **7** (180 mg).

Chromatographically pure samples of commonly occurring flavonoids (quercetin, rhamnetin, dihydroquercetin, quercetin 3-glycoside, quercetin 3′-glycoside, and isorhamnetin 3-glycoside), organic acids (benzoic, shikimic, and protocatechuic), and cyclitols (pinitol) were also isolated and identified during the preparative chromatography of compounds **1**–**7**. The identity of these compounds was established through direct comparison (spectral, physical, and chromatographic) with compounds in our laboratory.

Nuclear magnetic resonance (NMR) spectra were obtained by using a Varian EM-390. Mass spectra were obtained from a VG-micromass 70/70. Melting points are uncorrected.

Compound 1. Dihydro-*p*-coumaryl alcohol γ-*O*-acetate (oil). Found: C, 68.0; H, 7.92. $C_{11}H_{14}O_3$ requires C, 67.9; H, 7.90. NMR ($CDCl_3$) δ 1.90 (2 H, m, $CH_2CH_2CH_2$), 2.00 (3 H, s, O*Ac*), 2.56 (2 H, t, J = 7.0 Hz, $ArCH_2CH_2$), 4.03 (2 H, t, J = 7.0 Hz, CH_2CH_2OAc), 6.60 (1 H, br s, ArO*H*); 6.74 (2 H, d, J = 9.0 Hz, Ar*H*); 6.99 (2 H, d, J = 9.0 Hz, Ar*H*).

Compound 2. Dihydroconiferyl alcohol γ-*O*-acetate (oil). Found: C, 64.4; H, 7.21. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.19. NMR ($CDCl_3$) δ 1.90 (2 H, m, $CH_2CH_2CH_2$), 2.00 (3 H, s, O*Ac*), 2.56 (2 H, t, J = 7.0 Hz, $ArCH_2CH_2$), 3.82 (3 H, s, $ArOCH_3$), 4.05 (2 H, t, J = 7.0 Hz, CH_2CH_2OAc), 5.57 (1 H, s, ArO*H*), 6.56–6.87 (3 H, m, Ar*H*).

Compound 3. 2,3-Dihydro-7-hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)-3-(hydroxymethyl)-5-benzofuranpropanol (impure, amorphous). NMR (acetone-d_6) δ 1.74 (2 H, m, $CH_2CH_2CH_2$), 2.54 (2 H, t, J = 6.5 Hz, $ArCH_2CH_2$), 3.53 (2 H, t, J = 6.5 Hz, CH_2CH_2OH), 3.79 (3 H, s, $ArOCH_3$), 3.7–4.07 [3 H, m, C*H*(Ar), CH_2OH], 5.48 [1 H, d, J = 6.0 Hz, ArC*H*(O)], 6.60 (2 H, br s, Ar*H*), 6.65–7.20 (3 H, m, Ar*H*).

Compound 12. Compound **3** was acetylated (Ac_2O/pyridine) and chromatographically purified (silica; hexane–acetone, 5:1) to yield **12** (oil). Found: M^+ 514.1836. $C_{27}H_{30}O_{10}$ requires M^+ 514.1839. NMR ($CDCl_3$) δ 1.93 (2 H, m, $CH_2CH_2CH_2$), 2.03 (3 H, s, CH_2OAc), 2.05 (3 H, s, CH_2OAc), 2.26 (3 H, s, ArO*Ac*), 2.60 (2 H, t, J = 7.0 Hz, $ArCH_2CH_2$), 3.53–3.78 (1 H, m, ArC*H*), 3.77 (3 H, s, $ArOCH_3$), 4.06 (2 H, t, J = 7.0 Hz, (CH_2OAc), 4.23 [1 H, q, J = 11.0, 0.5 Hz, C(*H*)HOAc], 4.44 [1 H, q, J = 11.0, 6.0 Hz, C(H)*H*OAc], 5.53 (1 H, d, J = 6.0 Hz, ArC*H*O), 6.73–7.08 (5 H, m, Ar*H*).

Compound 4. 1-(4-Hydroxy-3-methoxyphenyl)-2-[2-hydroxy-4-(3-hydroxypropyl)phenoxy]-1,3-propanediol (impure, amorphous). NMR (acetone-d_6) δ 1.78 (2 H, m, $CH_2CH_2CH_2$), 2.53 (2 H, t, J = 7.5 Hz, $ArCH_2CH_2$), 3.54 (2 H, t, J = 7.0 Hz, CH_2CH_2OH), 3.78 (3 H, s, $ArOCH_3$), 3.7–4.1 [3 H, m, C*H*(OAr), CH_2OH], 4.95 [1 H, d, J = 4.0, ArC*H*(OH)], 6.5–7.1 (6 H, m, Ar*H*).

Compound 13. Compound **4** was acetylated (Ac_2O/pyridine) and chromatographically purified (silica; hexane–acetone, 5:1) to yield **13** (oil). Found: M^+ 574.2056. $C_{29}H_{34}O_{12}$ requires M^+ 574.2050. NMR ($CDCl_3$) δ 1.92 (2 H, m, $CH_2CH_2CH_2$), 1.94, 2.00, 2.08, 2.13, 2.27 (3 H, s, CH_2OAc and ArO*Ac*), 2.57 (2 H, t, J = 7.5 Hz, $ArCH_2CH_2$), 3.78 (3 H, s, $ArOCH_3$), 4.05 (2 H, t, J = 6.5 Hz, CH_2OAc), 4.06, [1 H, q, J = 5.0, 13 Hz, C(H)*H*OAc], 4.34 [1 H, q, J = 6.0, 13 Hz, C(*H*)HOAc], 4.66 (1 H, q, J = 4.5, 6.0 Hz, ArO*CH*), 5.99 (1 H, d, J = 4.5 Hz, ArC*H*OAc), 4.7–7.0 (6 H, m, Ar*H*).

Compound 5. Dihydro-*p*-coumaryl alcohol γ-*O*-glucoside (mp 164–165 °C). Found: C, 57.4; H, 7.10. $C_{15}H_{22}O_7$ requires C, 57.3; H, 7.06. NMR (CD_3OD) δ 1.86 (2 H, m, $CH_2CH_2CH_2$), 2.57 (2 H, t, J = 7.5 Hz, $ArCH_2CH_2$), 3.20–3.95 (8 H, m, CH_2–O-*glucose*), 4.27 [1 H, d, J = 7.0 Hz, glucose C(1)], 4.72 (4 H, br, OH), 6.77 (2 H, d, J = 8.0 Hz, Ar*H*), 7.00 (2 H, d, J = 8.0 Hz, Ar*H*).

Compound 6. Dihydroconiferyl alcohol γ-*O*-glucoside (amorphous). Found: M^+ 344.1476. $C_{16}H_{24}O_8$ requires M^+ 344.1471. NMR (acetone-d_6) δ 1.83 (2 H, m, $CH_2CH_2CH_2$), 2.60 (2 H, t, J = 7.0 Hz, $ArCH_2CH_2$), 3.2–4.0 (8 H, m, CH_2–O-*glucose*), 3.80 (3 H, s, $ArOCH_3$), 4.29 [1 H, d, J = 7.0 Hz, glucose C(1)], 4.15–4.50 (3 H, br m, glucose OH), 6.6–6.9 (3 H, m, Ar*H*).

Compound 14. Compound **5** was acetylated (Ac_2O/pyridine) to yield **14** (oil). Found: M^+ 524.1898. $C_{25}H_{32}O_{12}$ requires M^+ 524.1894. NMR ($CDCl_3$) δ 1.92 (2 H, m, $CH_2CH_2CH_2$), 2.0–2.2 (12 H, ms, glucose-O*Ac*), 2.31 (3 H, s, ArO*Ac*), 2.67 (2 H, t, J = 7.0 Hz, $ArCH_2CH_2$), 4.33 (2 H, m, glucose CH_2), 4.57 [1 H, d, J = 7.0 Hz, glucose C(1)], 5.0–5.4 (3 H, m, glucose CH), 7.07 (2 H, d, J = 9.0 Hz, Ar*H*), 7.31 (2 H, d, J = 9.0, Ar*H*).

Compound 15. Compound **6** was acetylated (Ac_2O/pyridine) to yield **15** (mp 113–115 °C, methanol). Found: C, 56.3; H, 6.29. $C_{26}H_{34}O_{13}$ requires C, 56.3; H, 6.18. NMR ($CDCl_3$) δ 1.92 (2 H, m, $CH_2CH_2CH_2$), 2.0–2.4 (12 H, ms, glucose-O*Ac*), 2.33 (3 H, s, ArO*Ac*), 2.69 (2 H, t, J = 7.0 Hz, $ArCH_2CH_2$), 3.88 (3 H, s, $ArOCH_3$), 4.3 (2 H, m, glucose CH_2), 4.59 [1 H, d, J = 7.5 Hz, glucose C(1)], 5.0–5.4 (3 H, m, glucose CH), 6.7–7.2 (3 H, m, Ar*H*).

Compound 7. 2,3-Dihydro-7-hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)-3-(*O*-rhamnosylmethyl)-5-benzofuranpropanol (amorphous). Found: M^+ 492.1991. $C_{25}H_{32}O_{10}$ requires M^+ 492.1996. NMR (acetone-d_6) δ 1.18 (3 H, d, J = 6.0 Hz, rhamnose CH_3), 1.78 (2 H, m, $CH_2CH_2CH_2$),

2.53 (2 H, t, J = 6.5 Hz, ArCH_2CH$_2$), 3.53 (2 H, t, J = 6.5 Hz, CH$_2$O), 3.3–4.0 (8 H, CH_2–O–*rhamnose*), 4.10 (1 H, m, OH or *rhamnose*); 5.37 [1 H, br s, rhamnose C(1)], 5.55 [1 H, d, J = 6.0 Hz, ArCH(O)], 6.60 (2 H, s, ArH), 6.7–7.2 (3 H, m, ArH).

Compound 16. Compound 7 was acetylated (Ac_2O/pyridine) to yield 16 (oil). NMR ($CDCl_3$) δ 1.20 (3 H, d, J = 6.0 Hz, rhamnose methyl), 1.95 (2 H, m, CH$_2$CH_2CH$_2$), 1.92, 1.95, 2.00 (3 H, s, rhamnose–O*Ac*), 2.12 (3 H, s, CH$_2$O*Ac*), 2.23, 2.25 (3 H, s, ArO*Ac*), 2.53 (2 H, t, J = 7.5 Hz, ArCH_2CH$_2$), 3.80 (3 H, s, ArOCH_3), 3.5–3.95 (3 H, m, ArCH and CH_2–O–rhamnose), 4.08 (2 H, t, J = 6.0 Hz, CH_2OAc), 4.80 [or s, rhamnose C(1)], 5.04–5.35, (3 H, m, rhamnose–HOAc), 5.62 [1 H , d, J = 5.0 Hz, ArCH(O)], 6.7–7.2 (5 H, m, ArH).

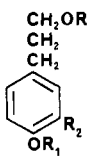
Hydrolysis of Compounds 5, 6, and 7. Compounds 5, 6 (30 mg), and 7 (40 mg) were each treated with 1% oxalic acid (5 mL) for 1 h at 100 °C. The hydrolysis mixture was cooled and extracted with ethyl acetate (10 mL). The aqueous layer was neutralized (saturated $NaHCO_3$), concentrated, and spotted on a paper chromatogram. Known sugars were also applied to the chromatogram, and after development (1-butanol–pyridine–water, 6:4:3) and spraying (*p*-anisidine/HCl), the hydrolysates and standards were compared. The hydrolysates of 5 and 6 contained glucose while the hydrolysate of 7 showed a positive comparison to rhamnose.

The ethyl acetate portion of the 7 hydrolysis was dried (Na_2SO_4) and concentrated to yield 3, directly comparable to the previously isolated compound chromatographically and spectrally.

RESULTS

Compounds 1–7 were isolated from the needles of Ponderosa pine in yields of less than 0.1% of the total acetone extract. Compounds 3, 4, 5, and 6 have been previously reported to occur in the needles of *Pinus contorta* (Higuchi et al., 1977; Higuchi and Donnelly, 1977, 1978) and *Pinus sylvestris* (Popoff and Theander, 1975, 1977). Characterization of compounds 3–6 in Ponderosa pine was established by comparison of their physical, spectral, and chromatographic properties with the published data. Compounds 1, 2, and 7 have not been previously reported to occur naturally although the 4-*O*-γ-D-glucoside of compound 1 (8) has been reported in *P. contorta* needles (Higuchi and Donnelly, 1977). Several glycosides of 2,3-dihydrobenzofuranpropanol dilignols have been reported in pine needles (Popoff and Theander, 1975, 1977) and western red cedar leaves (Manners and Swan, 1977).

Compounds 1 and 2 display NMR resonances for alkyl

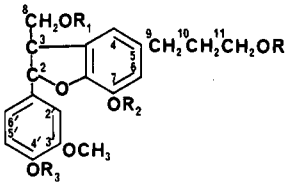


1, R = Ac; R_1, R_2 = H
2, R = Ac; R_1 = H; R_2 = OCH_3
5, R = glucose; R_1 = H; R_2 = H
6, R = glucose; R_1 = H; R_2 = OCH_3
8, R = Ac; R_1 = glucose; R_2 = H
9, R = Ac; R_1 = glucose; R_2 = OCH_3
14, R = glucose (OAc)$_4$; R_1 = Ac; R_2 = H
15, R = glucose (OAc)$_4$; R_1 = Ac; R_2 = OCH_3

acetates (δ 2.0), benzylic methylenes (δ 2.56), alkyl methylenes (δ 1.90), and acetyl methylenes (δ 4.03 and 4.05). These resonances are quickly associated to a phenylpropanol acetate structure. The close comparability of the NMR and physical data of 1 with the data for the hydrolysis product of 8 establishes 1 as dihydro-*p*-coumaryl alcohol γ-*O*-acetate.

The NMR spectral character of compound 2 differs from that of 1 only in the appearance of an aromatic methoxyl (δ 3.82) and one less aromatic proton. These spectral data and the prominent occurrence of similar dihydroconiferyl derivatives in other pines constitute strong evidence for the designation of 2 as dihydroconiferyl alcohol γ-*O*-acetate.

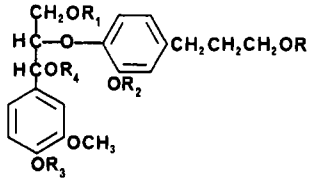
Compounds 3 and 4 were characterized as chromato-



3, R, R_1, R_2, R_3 = H
7, R = H; R_1 = rhamnose; R_2, R_3 = H
10, R = rhamnose; R_1, R_2, R_3 = H
11, R, R_1, R_3 = H; R_2 = rhamnose
12, R, R_1, R_2, R_3 = Ac
16, R, R_2, R_3 = Ac; R_1 = rhamnose (OAc)$_3$

graphically pure acetate derivatives (12; 13). Compound 12 shows NMR resonances for two alkyl and two aromatic acetates and phenylpropanol acetate methylenes as observed in compounds 1 and 2. These methylenes and the low-field (δ 5.53) methine doublet suggest a 2,3-dihydrobenzofuranpropanol dilignol. Comparison of the NMR data with that reported by Popoff and Theander (1977) for the acetylated derivative of hydrolyzed 10 shows close agreement and confirms the structural designation for the compound as 3.

Compound 13 displays three alkyl and two aromatic



4, R, R_1, R_2, R_3 = H
13, R, R_1, R_2, R_3 = Ac

acetate resonances in the NMR. The compound also shows the distinctive phenylpropanol acetate NMR resonances of 1 and 2. The low-field benzyl acetate methine (δ 5.99) and a second low-field phenoxy methine (δ 4.66) suggest 13 to be a 2-(phenoxypropanol)phenylpropanol dilignol. Comparison of the NMR data with that reported for the acetate derivative of 4 (Popoff and Theander, 1975) shows close agreement and establishes structure 4 for this compound from Ponderosa pine needles.

Compounds 5 and 6 display NMR resonances similar to those of 1 and 2 with the exception of a lack of acetate resonances and no low-field propanol acetate methylene resonances. Hydrolysis of both compounds yields glucose while the NMR of their acetate derivatives (14; 15) shows a single aromatic acetate for each compound. These data and the close comparability of the physical and spectral data with published observations (Higuchi et al., 1977) establish compounds 5 and 6 as dihydro-*p*-coumaryl alcohol γ-*O*-glucoside and dihydroconiferyl alcohol γ-*O*-glucoside, respectively.

Compound 7 has prominent NMR resonances for rhamnosyl methyl (δ 1.18), phenylpropanol methylenes (δ 1.78, 2.53, and 3.53), and benzyl methine (δ 5.55). These resonances are consistent with similar signals observed for

2,3-dihydrobenzofuranpropanol dilignols (10; 11) reported in *P. sylvestris* (Popoff and Theander, 1977) and *Thuja plicata* (Manners and Swan, 1971, 1977). Hydrolysis of 7 yields rhamnose and 3.

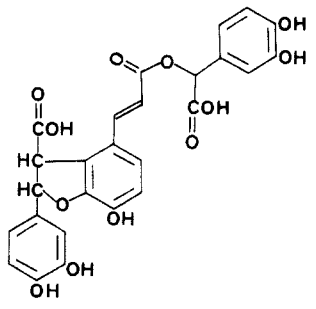
The position of rhamnose substitution in 7 was established through the examination of the NMR spectrum of the compound's acetate derivative (16). Four alkyl acetates [δ 1.9–2.0 (3), and 2.12] and two aromatic acetates (δ 2.23 and 2.25) dictate rhamnose substitution at C(8) or C(11). A comparison of chemical shifts of the propanol acetate methylene [C(8)] (δ 4.02) with similar methylenes observed in compounds 1, 2, and 12 and the collapse of this resonance upon the irradiation of the δ 1.95 methylene multiplet establish rhamnose substitution at C(8). Compound 7 is therefore defined as 2,3-dihydro-7-hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)-3-(*O*-rhamnosylmethyl)-5-benzofuranpropanol.

DISCUSSION

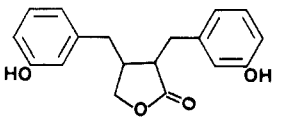
None of the water-soluble lignols identified in this investigation have yet been isolated in amounts sufficient for biological evaluation as potential abortifacients. In the absence of such biological data, the relative occurrence and structural character of the identified compounds in relation to known abortifacient agents suggest the types of water-soluble pine needle constituents which may be worthy of further consideration as potential abortifacients.

The ubiquitous occurrence of the flavonoids, organic acids, and cyclitol identified in this investigation in both toxic and nontoxic plant tissues suggests their unlikely candidacy as abortion causative agents in Ponderosa pine needles. Similarly, compounds 1, 2, 5, and 6 constitute common phenylpropane compounds restricted in natural occurrence only by minor differences in derivatization. The basic, commonly occurring, phenylpropane character of these compounds would also seem to eliminate their consideration as abortifacient agents in the pine needles.

In contrast, the dilignols (3; 4) and the new dilignol rhamnoside (7) are representative of a group of compounds thus far restricted in occurrence to *P. sylvestris*, *P. contorta*, *P. ponderosa*, and *T. plicata*. Compounds 4 and 7 also are structurally similar to a water-soluble 2,3-dihydrobenzofuran derivative, lithospermic acid (17), isolated



17



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from *Lithospermum ruderale* roots (Kelly et al., 1975), which has been shown to possess antigonadotropic activity (Breneman et al., 1976). The biological activity of lithospermic acid requires its oxidation, possibly to an active *o*-benzoquinone, and such activity is enhanced by the presence of quercetin glycosides (Wagner et al., 1970). The co-occurrence of the dilignol (4) and its rhamnoside (7) with quercetin and its glycosides and the potential ability of 4 to be oxidized to a reactive *p*-quinone methide suggests the possible participation of these compounds in the observed abortifacient activity of the pine needles.

The biological activity of natural dilignols in large animals has yet to be verified. However, structurally related dibenzylbutrolactone lignans (18), recently isolated from human (Setchell et al., 1980b) and veret monkey urine (Setchell et al., 1980a), have been suggested to be associated with luteolytic activity and the regulation of the length of the luteal phase of the menstral cycle. Such verification is severely limited by the natural availability of these compounds, and initial bioassay experiments may be restricted to the examination of more readily available dihydrobenzofuran compounds with closely related structures.

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