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ISOPRENYLATED RESORCINOL DERIVATIVES FROM *GLYCYRRHIZA ACANTHOCARPA*

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Key Word Index—*Glycyrrhiza acanthocarpa*; Leguminosae; resorcinols; isoprenylated derivatives.

Abstract—The ether extract of leaves and terminal branches of *Glycyrrhiza acanthocarpa* afforded four new isoprenylated resorcinol derivatives. Two of these are isoprenologues of cannabigerol and cannabigerolic acid.

INTRODUCTION

The genus *Glycyrrhiza*, whose roots provide liquorice, has attracted attention as a source of flavonoids and of anti-inflammatory triterpene acids. *G. acanthocarpa* (Lindl) J. M. Black, the only described species of this genus in Western Australia [1], is a low spreading, viscid shrub which regenerates rapidly on roadsides in the Kalgoorlie Goldfield region of Western Australia. We have investigated the components of the aerial parts of this plant and this report describes the structure of the compounds isolated.

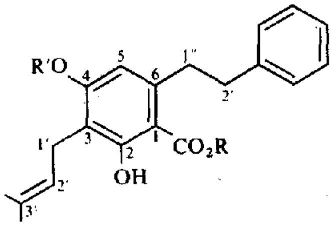
RESULTS AND DISCUSSION

The acidic fraction from an ether extract of *G. acanthocarpa* yielded, after chromatography on silicic acid, the crystalline dihydrostilbene acid **1**, $C_{21}H_{24}O_4$, which on treatment with CH_2N_2 gave the methyl ester **2**, $C_{22}H_{26}O_4$. The structure assigned to **1** followed from an analysis of the spectroscopic data. The ^{1}H NMR spectrum showed signals indicative of a phenylethyl group (δ 7.23, 5 aromatic protons; δ 2.91 and 3.26, AA′BB′ system). The presence of a second aromatic ring was suggested by a signal for a proton at δ 6.32. Resonance signals were also apparent due to a methoxy group (δ 3.77) and a 3-methylbut-2-enyl system, the component signals of which were assigned by NMDR. Two exchangeable protons (δ 8.5) were assigned to a hydroxylic and a carboxylic acid proton. The low frequency of IR absorption bands for these groups (ν_{max} 3300, 2660–2520 and 1640 cm^{-1}) suggested hydrogen bonding between them and the presence of a salicylic acid moiety was supported by the UV spectrum of **1** [λ_{max} nm (ε): 220 (16 900), 260 (4100) and 300 nm (2100)] which was consistent with the absorption of a 2-hydroxy-4-methoxy benzoic acid group [2]. Further information about the relative orientation of substituents on the second aromatic ring was obtained as follows. Treatment of the methyl ester **2** under acidic conditions gave the chroman **3** whereas the acid **1** under similar conditions yielded the chroman **4** which had undergone decarboxylation. In the ^{1}H NMR spectrum of **4** the newly introduced aromatic proton (δ 6.28) appeared as a doublet ($J = 1.5$ Hz) and must be *meta* to the other aromatic proton which in turn showed an NOE of 14 % when the methoxyl protons were irradiated in compound **1**. These results allow the placement of the carboxylic acid, hydroxyl and isoprenyl groups in a contiguous manner, and of the two possibilities now remaining that which places the methoxyl group *para* to the carboxylic acid group is preferred on the basis of UV evidence and on biogenetic grounds. (The alternative structure would contain a 2-hydroxy-6-methoxybenzoic acid chromophore; UV λ_{max}^{EtOH} nm (ε): 213 (17 800), 251 (7350), 331 (3500) [2].) Furthermore, the relative deshielding of one of the benzylic methylene groups is explained by the presence of an *ortho*-carboxylic acid group.

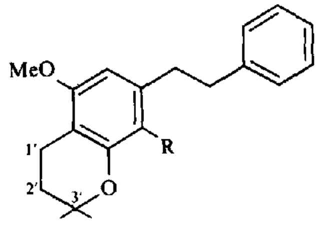
A second crystalline compound ($C_{18}H_{26}O_4$) isolated from the acidic fraction was shown to be 2-hydroxy-4-methoxy-3(3-methyl-2-but-2-enyl)-6-(1-pentyl)benzoic acid (**5**). The IR and UV spectra of this compound and its methyl ester (**6**) were essentially similar to those of **1** and **2**. The ^{1}H NMR spectrum of **4** lacked signals attributed to the phenylethyl group of **1** and showed resonances for a pentyl chain (δ 0.89, *t*(*br*), $-CH_2-C\underline{H}_3$; 1.26, *m*, 6 H, and 2.92, *m*, benzylic-CH_2). The spectroscopic data for the derived methyl ester **6** and decarboxylated chroman (**7**) were consistent with the structure proposed.

Separation of the components of the neutral fraction from *G. acanthocarpa* allowed the isolation of four compounds. The two less polar ones were separated from each other by preparative TLC and were obtained as oils. Analysis of their spectroscopic data showed them to be the decarboxylated analogues of **1** and **5** and they were assigned structures **8** and **9** respectively. This was confirmed by treatment of each one under acidic conditions which gave the chromans **4** and **7** identical to those obtained from **1** and **5**. The two more polar components were obtained as a crystalline fraction and could be separated after acetylation and fractional crystallization. They were identified as *ent*-3β,17,19-triacetoxy-16β-(−)-kaurane [3] and *ent*-3β,17-diacetoxy-16α-(−)-kauran-16-ol [4] by comparison with authentic samples.

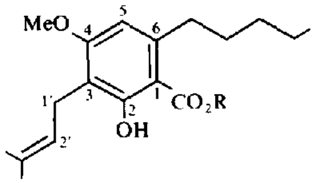
Although a number of bibenzyl compounds have been identified in nature only a few contain the salicyclic acid moiety and a prenyl side chain [5]. Recently, Bohlmann and Hoffmann [6] reported the isolation of a number of



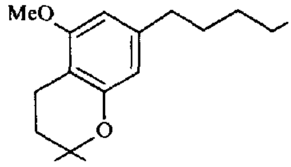
1 R = H, R' = Me
2 R = Me, R' = Me
10 R = H, R' = H



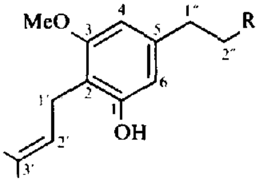
3 R = CO_2Me
4 R = H



5 R = H
6 R = Me



7



8 R = Ph
9 R = $-(CH_2)_2-Me$

derivatives of **10** from *Helichrysum umbraculigerum*, together with variants containing a geranyl moiety. Asakawa *et al.* [7] isolated a dihydrostilbene corresponding to **10** and a decarboxylated analogue corresponding to **8** from *Radula complanata* but did not fully characterize these compounds. The pentyl-substituted resorcinols (**4** and **8**) are isoprenyl analogues of cannabigerolic acid and cannabigerol [8] and do not appear to have been isolated previously.

EXPERIMENTAL

General experimental details have been described previously [9].

Extraction and isolation of components of Glycyrrhiza acanthocarpa. Dried, crushed plant (950 g), collected in the Kalgoorlie Goldfields in Western Australia, was extracted with Et_2O and the ethereal soln was partitioned between 7% aq. $NaHCO_3$ and 5% aq. NaOH. The material (14 g) recovered from the NaOH fraction was adsorbed on a column of silicic acid. Elution with petrol–EtOAc (17:3) gave an oil (5 g) which from TLC (HOAc–EtOAc–petrol, 1:20:79) appeared to be a mixture of **1** and **5** and a large amount of fatty acids. The oil was partitioned between $MeOH–H_2O$ (19:1) and petrol. The MeOH-soluble fraction (2 g) in MeOH was stored at 0° for 2 days and after removal of the waxy ppt. the soln was heated and saturated with urea and allowed to cool after which the crystalline urea complex was filtered. This process was repeated until only crystalline urea was recovered. A portion (300 mg) of this defatted material was separated by prep TLC yielding:

(a) *2-Hydroxy-4-methoxy-3-(3-methylbut-2-enyl)-6-(2-phenylethyl) benzoic acid* (**1**) (140 mg) which was recrystallized from toluene–petrol as needles, mp 134° (Found: C, 73.89; H, 7.14. $C_{21}H_{24}O_4$ requires: C, 74.09; H, 7.11%). IR $\nu_{max}^{CS_2}$ cm^{-1}: 3300 (OH), 2660, 2600, 2520 (OH), 1640 ($-CO_2H$); UV λ_{max}^{MeOH} nm (ε): 220 (16 900), 260 (4100), 300 (2100), unchanged on addition of 1% NaOH soln; ^1H NMR ($CDCl_3$; 90 MHz): δ 7.23 (*s*, aromatic H's), 6.32 (*s*, 5-H), 5.21 (*t* (*br*), *J* = 7.5 Hz, 2'-H), 3.77 (*s*, $-OCH_3$), 3.34 (*d* (*br*), *J* = 7.5 Hz, 1'-H_2), 3.26 and 2.91 (AA'BB' system, 1''- and 2''-H_2), 1.79 and 1.62 (*s* (*br*), 3'-$(Me)_2$); MS *m/z* (rel. int.): 340 $[M]^+$ (42), 322 (22), 307 (40), 279 (33), 267 (29), 238 (20), 193 (29), 145 (22), 91 (100).

(b) *2-Hydroxy-4-methoxy-3-(3-methylbut-2-enyl)-6-(1-pentyl) benzoic acid* (**5**) (100 mg) which was recrystallized from pentane as needles, mp 102–103° (Found: C, 70.37; H, 8.46. $C_{18}H_{26}O_4$ requires: C, 70.56; H, 8.55%). IR $\nu_{max}^{CS_2}$ cm^{-1}: 3300 (OH), 2700, 2610, 2560 (OH), 1650 ($-CO_2H$); UV λ_{max}^{MeOH} nm (ε): 220 (22 900), 258 (5500), 300 (2700) (unchanged on addition of 1% NaOH soln); ^1H NMR ($CDCl_3$, 90 MHz): 6.28 (*s*, 5-H), 5.19 (*t* (*br*), *J* = 7.5 Hz, 2'-H), 3.86 (*s*, $-OCH_3$), 3.32 (*d* (*br*), *J* = 7 Hz, 1'-H_2), 2.92 (*m*, 1''-H_2), 1.77 and 1.66 (*s* (*br*), 3'-$(Me)_2$), 1.26 (*m*, 6 H), 0.89 (*t* (*br*), $-CH_2-CH_3$); MS *m/z* (rel. int.): 306 $[M]^+$ (50), 288 (100), 263 (59), 245 (92), 233 (91), 204 (88).

The neutral fraction (14 g) of the extract was adsorbed on a column of Al_2O_3 (neutral, act III). Elution with $CHCl_3$–petrol (3:17) gave an oil (6 g) which from TLC appeared as a mixture of two compounds. Prep. TLC of a portion of this yielded:

(a) 3-*Methoxy*-2-(3-*methylbut*-2-*enyl*)-5-(1-*pentyl*)*phenol* (**9**) as an oil, bp 150° (bath/0.1 mm) (Found: C, 77.53; H, 9.72. $C_{17}H_{26}O_2$ requires: C, 77.82; H, 9.99 %). IR ν_{max}^{Film} cm^{-1}: 3460 (OH), 1615, 1590, 1510; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 6.30 (*s*, 4′-H), 5.34 (exchangeable H and *t* (*br*), *J* = 7 Hz, 2′-H), 3.79 (*s*, –OMe), 3.37 (*d* (*br*), *J* = 7 Hz, 1′-H_2), 2.51 (*t* (*br*), *J* = 7 Hz, 1″-H_2), 1.88 and 1.73 (*s* (*br*), 3′-$(Me)_2$), 1.26 (*m*, –$(CH_2)_3$), 0.90 (*t* (*br*), *J* = 7 Hz, –CH_2—$C\underline{H}_3$); MS *m/z* (rel. int.): 262 $[M]^+$ (77), 247 (53), 207 (100), 177 (14), 150 (85).

(b) 3-*Methoxy*-2-(3-*methylbut*-2-*enyl*)-5-(2-*phenylethyl*)*phenol* (**8**) as an oil (Found: M^+ 296.1788. $C_{20}H_{24}O_2$ requires: M^+ 296.1776). IR ν_{max}^{Film} cm^{-1}: 3420 (OH), 1620, 1600, 1515, 700; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 7.24 (*m*, aromatic H's), 6.34 and 6.28 (*d*, *J* = 1.5 Hz, 4- and 6-H), 5.23 (exchangeable H and *t* (*br*), *J* = 7.5 Hz, 2′-H), 3.75 (*s*, –OMe), 3.36 (*d* (*br*), *J* = 7.5 Hz, 1′-H_2), 2.86 (*m*, 1″- and 2″-H_2), 1.80 and 1.73 (*s*, 3-Me); MS *m/z* (rel. int.): 296 (74), 281 (26), 241 (100), 205 (81), 150 (37), 137 (26), 105 (34), 91 (95).

Elution with EtOAc gave a crystalline fraction (100 mg) which was treated with Ac_2O–pyridine. The derived acetates were separated by prep. TLC ($CHCl_3$) to yield:

(a) ent-3β,17,19-*Triacetoxy*-16β-(–)-*kaurane*, mp 123–124°, $[\alpha]_D$ –47° (*c* 1.5) (lit. [3] mp 126°, $[\alpha]_D$ –52°), mmp with an authentic sample, 123–124.5°.

(b) ent-3β,17-*Diacetoxy*-16α-(–)-*kauran*-16-*ol*, mp 184–185°, $[\alpha]_D$ –42° (*c* 0.9) (lit. [4] mp 186–187°, $[\alpha]_D$ –48°, mmp with an authentic sample 184–185°.

Separation of the methyl esters of **1** *and* **5**. A portion (500 mg) of defatted material obtained as described above was treated with CH_2N_2 in Et_2O. The product recovered was separated by prep. TLC (petrol, multiple development) to give:

(a) *Methyl ester of* **1** (**2**) (200 mg) which crystallized from pentane as needles, mp 75–76° (Found: C, 74.58; H, 7.75. $C_{22}H_{26}O_4$ requires: C, 74.55; H, 7.39 %). IR $\nu_{max}^{CS_2}$ cm^{-1}: 3300 (OH), 1670 (—CO_2Me); ^{1}H NMR ($CDCl_3$, 90 MHz): δ 11.75 (exchangeable H, –OH), 7.23 (*s*, aromatic H's), 6.19 (*s*, 5-*H*), 5.21 (*t* (*br*), *J* = 7 Hz, 2′-H), 3.93 and 3.77 (*s*, 2 × OMe), 3.34 (*d* (*br*), *J* = 7 Hz, 1′-H_2), 3.13 and 2.96 (AA′BB′ system, 1″- and 2″-H_2), 1.78 and 1.67 (*s* (*br*), 3′–$(Me)_2$); MS (*rel. int.*): 354 $[M]^+$ (61) 322 (42), 307 (61), 279 (39), 267 (45), 91 (100).

(b) *Methyl ester of* **5** (**6**) (180 mg) which crystallized from pentane as needles, mp 50–51° (Found: M^+ 320.2009. $C_{19}H_{28}O_4$ requires: M^+ 320.1987). IR $\nu_{max}^{CS_2}$ cm^{-1}: 3450 (OH), 1660 (–CO_2Me). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 11.70 (exchangeable H, –OH), 6.62 (*s*, 5-H), 5.21 (*t* (*br*), *J* = 7 Hz, 2′-H), 3.89 and 3.83 (*s*, 2 × –$OC\underline{H}_3$), 3.33 (*d* (*br*), *J* = 7 Hz, 1′-H_2), 2.86 (*m*, 1″-H_2), 1.77 and 1.66 (*s* (*br*), 3′–$(Me)_2$), 1.26 (6 H, *m*), 0.90 (*t* (*br*), *J* = 7 Hz, –CH_2–$C\underline{H}_3$); MS (rel. int.): *m/z* 320 $[M]^+$, 288, 276, 245, 233. Both acids (**1** and **5**) could be methylated with CH_2N_2 to the corresponding methyl esters (**2** and **6**).

Formation of chromans. A sample of **2** (70 mg) in THF (50 ml) was treated with *p*-TsOH (5 g) and the mixture was refluxed for 18 hr. The product recovered was purified by prep. TLC ($CHCl_3$–hexane, 1:4) to give the chroman **3** (31 mg) which crystallized from hexane as fine needles, mp 112.5–114.5° (Found: C, 75.07; H, 7.55. $C_{22}H_{26}O_4$ requires: C, 74.55; H, 7.39 %). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 7.21 (*m*, aromatic H's), 6.11 (*s*, 5-H), 3.86 and 3.73 (*s*, 2 × –OMe), 2.85 (*m*, 1″- and 2″-H_2), 2.59 (*t* (*br*), *J* = 7 Hz, 1′-H_2), 1.76 (*t* (*br*), 2′-H_2), 1.29 (*s*, 3′-$(Me)_2$); MS *m/z* (rel. int.): 354 $[M]^+$, (44), 323 (17), 299 (36), 267 (64), 265 (40), 263 (40), 233 (48), 207 (25), 149 (24), 91 (100).

The dihydrostilbene acid **1** (10 mg) under the same conditions as above yielded the decarboxylated chroman **4** as an oil, bp 100° (bath)/0.01 mm) (Found: M^+ 296.1791. $C_{20}H_{24}O_2$ requires: M^+ 296.1776). IR ν_{max} cm^{-1}: 1620, 1600; ^{1}H NMR ($CDCl_3$, 80 MHz): δ 7.23 (*s*, aromatic H's), 6.35 and 6.28 (*d*, *J* = 1.5, 4- and 6-H), 3.86 (*s*, –OMe), 2.86 (*m*, 1″- and 2″-H_2), 2.61 (*t* (*br*), 1′-H_2), 1.75 (*t* (*br*), 2′-H_2), 1.31 (*s*, 3′-$(Me)_2$); MS *m/z* (rel. int.): 296 $[M]^+$ (65), 281 (11), 241 (100), 205 (49), 150 (27), 91 (76).

5 (10 mg) was treated as for **2** to give the decarboxylated chroman **7** as an oil, bp 158° (bath/0.1 mm) (Found: C, 77.88; H, 9.88. $C_{17}H_{26}O_2$ requires: C, 77.82; H, 9.99 %). ^{1}H NMR ($CDCl_3$, 80 MHz): δ 6.30 and 6.21 (*d*, *J* = 1.4 Hz, 4- and 6-H), 3.80 (*s*, –OMe), 2.60 (*m*, 1′- and 1″-H_2), 1.31 (*s*, 3′-$(Me)_2$), 1.27 (6 H, *m*, $(CH_2)_3$), 0.89 (*t* (*br*), –CH_2–$C\underline{H}_3$); MS *m/z* (rel. int.): 262 (50), 247 (17), 219 (9), 207 (100), 206 (76), 176 (12), 163 (15), 150 (78), 91 (38).

Separate treatment of **8** and **9** under conditions described for **2** yielded **4** and **7** respectively, identical in all respects with the chromans obtained from **1** and **5**.

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