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RANDAINOL: A NEOLIGNAN FROM *SASSAFRAS RANDAIENSE*

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Key Word Index—*Sassafras randaiense*, Lauraceae, randainal, 2,2'-dihydroxy-5-allylbiphenyl-5'-propenol, magnolol

Abstract—The novel neolignan randainol was isolated from the roots of *Sassafras randaiense* Its identity as 2,2'-dihydroxy-5-allylbiphenyl-5'-propenol was established on the basis of chemical and spectroscopic evidence together with correlation with magnolol (2,2'-dihydroxy-5,5'-diallylbiphenyl)

INTRODUCTION

Recently, we have reported [1] the occurrence of the two antimicrobial neolignans magnolol (**1**) and isomagnolol (**2**) in the roots of *Sassafras randaiense* (Hay) Rehd The presence [2] of randainal (**3**) and randaiol (**4**) in the heartwood of the same plant prompted us to re-examine the roots for similar compounds in order to test them for antimicrobial activity This investigation resulted in the isolation of an analogous primary alcohol that was named randainol (**5**)† This paper describes its isolation, characterization and synthesis

RESULTS AND DISCUSSION

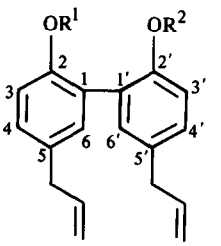
The mother liquor left from the crystallization of three crops of magnolol (**1**) isolated [1] from the roots of *S randaiense* was flash chromatographed [3] on silica gel using 7% ethanol in chloroform to yield **5** as a colorless oil, $C_{18}H_{18}O_3$ that decomposed quickly even at −20° The UV, ^{1}H NMR and IR spectra (see Experimental) established its aromatic nature together with the presence of an allyl and an *E*-propenol group Since **5** was too unstable to provide an adequate ^{13}C NMR spectrum, its more stable triacetate **6** was prepared and its ^{13}C NMR spectrum (see Experimental) was in agreement with its proposed structure

The structure of **5** was unambiguously confirmed by treating magnolol diacetate (**7**) with mercuric acetate [4] in acetic acid solution This provided a product identical with **6** but it was difficult to purify by flash chromatography [3] as it was contaminated with magnolol monoacetate (**8**) arising from partial decomposition of **7** This problem was circumvented by adding acetic anhydride to the reaction mixture The yield of the tetraacetate **9** was kept at a minimum by limiting the reaction time Lithium aluminum hydride reduction of **6** provided a product indistinguishable from natural **5**

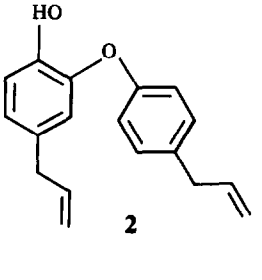
Attempted oxidation of randainol (**5**) to the analogous aldehyde randainal (**3**) using MnO_2, CrO_3 and polymer-supported pyridinium chlorochromate (PCC) [5] was unsuccessful This was apparently due to its instability and tendency to polymerize With PCC a poor yield of an aldehyde was obtained but its mass and ^{1}H NMR spectra suggested complete oxidation of the propenol group to yield the aromatic aldehyde **10**

EXPERIMENTAL

IR spectra were measured as 7–9% solns in $CHCl_3$ ^{1}H NMR spectra were recorded at 90 MHz using $CDCl_3$ as solvent and TMS as int standard, chemical shifts are reported in δ (ppm) units ^{13}C NMR spectra were measured at 15 03 MHz with chemical shifts also reported in δ (ppm) units UV spectra were measured in MeOH solns The plant material was collected and identified as previously reported [1]



1 $R^1 = R^2 = H$
7 $R^1 = R^2 = Ac$
8 $R^1 = H$, $R^2 = Ac$



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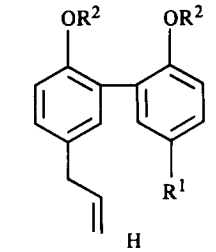
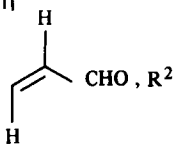
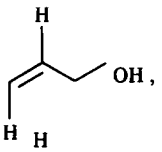
*Work completed while on leave at the Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

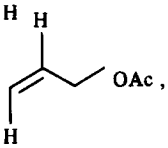
†Randainol (**5**), unlike magnolol (**1**) [1], exhibited only marginal antimicrobial activity against *Bacillus subtilis* and *Staphylococcal aureus* when qualitatitely examined using the procedure previously described [6]



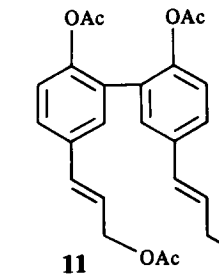
3 R^1 =  CHO, R^2 = H

4 R^1 = OH, R^2 = H

5 R^1 =  OH, R^2 = H

6 R^1 =  OAc, R^2 = Ac

10 R^1 = CHO, R^2 = H



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Isolation of randainol (**5**) The mother liquor (0 5 g) [1] left from the crystallization of three crops of magnolol (**1**) was flash chromatographed [3] on silica gel using 7% EtOH in $CHCl_3$ as solvent Randainol (**5**) (49 mg) was obtained as a colorless oil, homogeneous on TLC (R_f 0 55 on silica gel using the same solvent system), UV λ_{max}^{MeOH} 245 nm (ε = 3315) with shoulders at 270 nm (ε = 1939) and 285 (ε = 1481), IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3520 and 3250 (OH), 1628 (C=C) and 1595 (Ar C=C), ^{1}H NMR ($CDCl_3$) δ 1 90 (1H, *br s*, exchangeable, $-CH_2O\underline{H}$), 3 32 (2H, *d*, *J* = 7 0 Hz, $-C\underline{H}_2-CH=CH_2$), 4 25 (2H, *d*, *J* = 6 Hz, $-C\underline{H}_2OH$), 5 10 (2H, *m*, CH_2=C–), 6 05 (1H, *m*, $CH_2C\underline{H}=CH_2$), 6 18 (1H, *dt*, *J* = 16 5 Hz, *J* = 6 0 Hz, –CH(1)=C<u>H</u>(2)–CH_2(3)OH), 6 61 (1H, *d*, *J* = 16 5 Hz, –C<u>H</u>(1)=CH(2)–CH_2(3)OH), two phenolic exchangeable protons at 6 0 and 7 10; and 6 proton multiplet at δ6 8–7 4, MS *m/z* 282 (8%) $[M]^+$ (Found $[M]^+$ 282 3414 $C_{18}H_{18}O_3$ requires $[M]^+$ 282 3420)

Acetylation of randainol (**5**) *to* **6** Randainol (**5**) (100 mg) was stirred with 1 ml of pyridine and 1 ml of Ac_2O for 25 hr Usual work-up then flash chromatography [3] on silica gel using $CHCl_3$ as solvent provided **6** as a colorless oil, homogeneous on TLC (R_f 0 80 on silica gel using 5% EtOH in $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ no OH bands and intense band at 1750 cm^{-1} (AcO), ^{1}H NMR ($CDCl_3$) same pattern as in **5** but with three signals at δ2 02, 2 05 and 2 10 (3H each, *s*, AcO) and downfield shift of $-CH_2-O$ to δ4 75 (2H, *d*, *J* = 6 0 Hz), ^{13}C NMR ($CDCl_3$) δ170 6 (*s*), 169 3 (*s*) and 169 1 (*s*) (3 C=O), 147 9 (*s*) and 146 5 (*s*) (C-2 and C-2'), 137 8 (*s*), 134 2 (*s*), 131 0 (*s*) and 130 2 (*s*) (C-1, C-5, C-1' and C-5'), 136 9 (*d*), 132 9 (*d*), 131 2 (*d*), 129 4 (*d*), 129 2 (*d*), 126 9 (*d*), 124 0 (*d*), 122 5 (*d*) and 122 8 (*d*) (C-3, C-4, C-6, C-3', C-4', C-6', <u>C</u>H=CH_2, and <u>C</u>H=<u>C</u>H_2–CH_2OH), 116 2 (*t*, –CH=<u>C</u>H_2), 64 8 (*t*, –CH_2OH), 39 5 (*t*), (–<u>C</u>H_2–CH=CH_2) and 20 7 (*q*, <u>C</u>H_3COO), MS *m/z* 408 (7%) $[M]^+$ (Found C, 70 77, H, 6 02 $C_{24}H_{24}O_6$ requires C, 70 57, H, 5 92%)

Oxidation of magnolol diacetate (**7**) *to triacetylrandainol* (**6**) Method (a) magnolol-diacetate (**7**) (1 5 g), prepared as previously reported [7] was refluxed for 6 hr in a soln of $Hg(OAc)_2$ (1 5 g) in HOAc (10 ml) The crude product (1 65 g) yielded four fractions upon flash chromatography [3] on silica gel using $CHCl_3$ as solvent Fraction 1 consisted of 0 35 g of unreacted **7**, fraction 2 (0 31 g) of magnolol monoacetate (**8**), colorless oil, homogeneous on TLC (R_f 0 30 on silica gel using $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3530 (OH) and 1750 (AcO), ^{1}H NMR ($CDCl_3$) δ1 96 (3H, *s*, AcO), δ3 35 (4H, over *dd*, *J* = 7 0 Hz, 2 $C\underline{H}_2$–CH=CH_2), 4 98–5 32 (4H, *m*, over 2 CH_2–CH=C<u>H</u>$_2$), 5 85 (2H, *m*, 2 over CH_2–C<u>H</u>=CH_2) and 6 2–7 3 (6H, *m*, Ar–H), ^{13}C NMR ($CDCl_3$) same pattern as for **7** [9] but with acetate signals at 20 5 (*q*) and 169 8 (*s*) and two oxygenated Ar carbons at δ151 8 (*s*, C–OH) and 147 0 (C–OAc), MS, *m/z* 308 (7%) $[M]^+$ (Found C, 77 88, H, 6 57 $C_{20}H_{20}O_3$ [308] requires C, 77 90; H, 6 54%) identical with magnolol monoacetate (**8**) obtained by reacting magnolol (**1**) (798 mg) with one equiv of Ac_2O (306 mg) in 4 ml of pyridine (superimposable IR, ^{1}H NMR and MS), fraction 3 (0 87 g) of **6**, identical with randainol triacetate prepared above, fraction 4 (0 11 g) of **11**, homogeneous on TLC (R_f 0 11, silica gel using $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1} no OH bands, 1730 (–CH_2–O–CO–) and 1750 (Ar–O–CO–), ^{1}H NMR ($CDCl_3$) two 6H acetate singlets at δ2 05 and 2 11, 4 75 (4H, *d*, *J* = 7 0 Hz, –C<u>H</u>$_2$–OAc), 6 25 (2H, *dt*, *J* = 16 5 and 7 0 Hz, CH=C<u>H</u>–CH_2OAc), 6 68 (2H, *d*, *J* = 16 5 Hz, –C<u>H</u>=CH–CH_2OAc) and 7 1–7 6 (6H, *m*, Ar–H), ^{13}C NMR ($CDCl_3$) δ170 6 (*s*, CO), 169 0 (*s*, CO), 147 9 (Ar–<u>C</u>–OAc), 2*s* at δ134 4 and 130 7, 5 *d* at δ132 7, 129 4, 127 2, 124 2 and 122 9, δ64 8 (*t*, –<u>C</u>H_2OAc), 20 9 (*q*, <u>C</u>H_3COO) and δ20 7 (*q*, <u>C</u>H_3COO), MS *m/z* 466 (5%) (Found C, 66 87, H, 5 79 $C_{26}H_{26}O_8$ (466) requires C, 66 94, H, 5 62%) Method (b) same as for (a) but with the addition of 2 ml of Ac_2O gave virtually the same yield of **6** but without the formation of **8**, thus making the purification of **6** easier

Lithium aluminum hydride reduction of **6** *to randainol* (**5**) A soln of the triacetate **6** (200 mg) in Et_2O was added dropwise to a stirred soln of $LiAlH_4$ (400 mg) in 25 ml of Et_2O After 4 hr the mixture was worked up to provide 239 mg of an oil that was flash chromatographed on silica gel using 7% EtOH in $CHCl_3$ as solvent to provide a product (149 mg) indistinguishable from natural randainol (**5**) (superimposable IR and ^{1}H NMR spectra)

Attempted oxidation of randainol (**5**) *to randainol* (**3**) Randainol (**5**) (50 mg) was stirred for 24 hr in CH_2Cl_2 soln with 0 4 g of MnO_2 Work up provided only a few mg of residue due to irreversible adsorption and decomposition By using CrO_3 [8], a similar amount of randainol (**5**) provided a mixture of products (34 mg) none of which were aldehydes (TLC and ^{1}H NMR) The use of polymer-supported PCC [5] (200 mg) provided [from 50 mg of randainol (**5**)] 17 mg of a crude product that was flash chromatographed on silica gel using 6% EtOH in $CHCl_3$ as solvent to provide 6 mg of **10** as a colorless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3520 (OH) and 1690 (CHO), ^{1}H NMR ($CDCl_3$) same pattern as for **5** but with no signals due to a propenol moiety, instead, a signal at δ9 84 (1H, *s*, Ar–C<u>H</u>O) with two other downfield signals at δ7 80 (1H, *d*, *J* = 20 7 Hz, C_4 -H) and δ7 85 (1H, *s*, C_6 -H), MS *m/z* 254 (82%) $[M]^+$ (Found 254 2874 $[M]^+$ requires 254 2880)

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