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REVISED STRUCTURE FOR A NEOLIGNAN FROM *BRUCEA JAVANICA*

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Key Word Index—*Brucea javanica*; Simaroubaceae; 8-*O*-4′-neolignans; dilignols; guaiacylglycerol-*β*-coniferyl ether; ^{1}H and ^{13}C NMR spectra.

Abstract—On the basis of ^{1}H and ^{13}C NMR spectral comparison with natural and synthetic compounds, the neolignan isomers isolated from *Brucea javanica* for which unusual 8-*O*-6′-structures were proposed have been reassigned to the conventional 8-*O*-4′-structures (*erythro* and *threo*-guaiacylglycerol-*β*-coniferyl ether), respectively. Thus far, there is no evidence for the existence of 8-*O*-6′-neolignans in nature.

INTRODUCTION

Lignans and neolignans belong to an important group of optically active natural products consisting of two phenylpropane monomers linked through carbon–carbon or carbon–oxygen bonds [1]. In one class of neolignans, the phenylpropane monomers are linked through the 8-*O*-4′ atoms, as in formula **1**. Luyengi *et al.* [2] have isolated from *Brucea javanica* a mixture of neolignan isomers which were found to induce cell differentiation with human promyelocytic leukemia (HL-60) cells. They proposed the unusual structures **2** and **3**, ether-linked from C-8 to C-6′ rather than to C-4′, for the compounds on the basis of ^{1}H and ^{13}C NMR spectroscopy [2]. We have recently shown [3] that compounds isolated from *Arum italicum* for which similar unusual structures were proposed on the basis of NMR spectroscopy [4] were actually compounds **4** and **5**, isomers of the known 8-*O*-4′ neolignan guaiacylglycerol-*β*-coniferyl ether. Because the structures proposed for **2** and **3** represent linkages not previously found in neolignans, we undertook to synthesize compounds **4** and **5** and to compare their NMR spectra with those of the neolignan mixture. Herein we present evidence to show that the compounds isolated from *Brucea javanica* are the known isomeric neolignans **4** and **5**, rather than compounds **2** and **3**, respectively.

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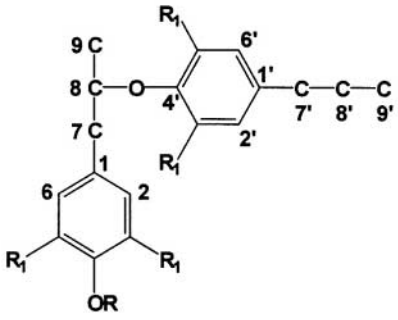
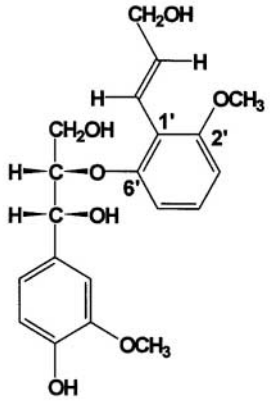
RESULTS AND DISCUSSION

Both *erythro* and *threo* neolignans **4** and **5** were prepared through a reaction sequence starting from the intermediate **6a**. Oxidation of **6a** with 2,3-dichloro-5,6-dicyanobenzoquinone using a modification [5] of a procedure used for the preparation of coniferaldehyde [6] gave the formylvinyl compound **6b**. Reduction of **6b** with sodium borohydride and subsequent alkaline hydrolysis gave rise to a mixture of *erythro* and *threo* neolignans **4** and **5**. Separation of **4** and **5** was achieved by ion exchange chromatography of their borate complexes, the *threo* isomer **5** eluting from the column in advance of the *erythro* isomer **4** [7]. NMR spectral comparison with related arylglycerol-*β*-aryl ethers examined by X-ray crystallography [8] provides unambiguous proof of the steric assignments of **4** and **5**. Compounds **4** and **5** are important substructures of lignin and they have been previously prepared as an isomeric mixture by two research groups [9, 10].

The ^{1}H and ^{13}C NMR spectral data for deuteriodimethylsulfoxide solutions of compounds **4** and **5** and those reported by Luyengi *et al.* [2] for the neolignan mixture of **2** and **3** are given in Tables 1 and 2, respectively. It is clear from Table 1 that, with the exception of the signals assigned to the hydroxyl protons, the ^{1}H NMR signals reported for the mixture of **2** and **3** are almost identical to those of the *erythro* 8-*O*-4′ neolignan **4** and are similar to those of the *threo* isomer **5**. Similarly, the ^{13}C NMR sig-



1 R = H or CH_3
R_1 = H or OCH_3



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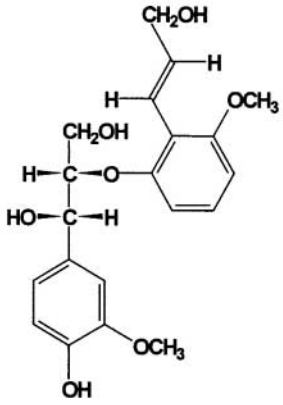

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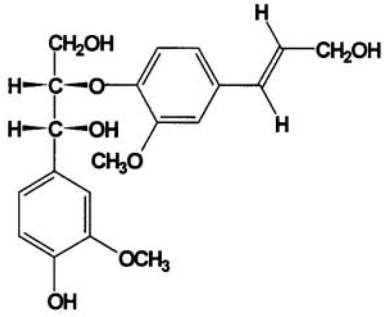

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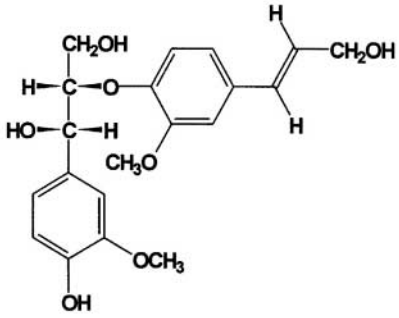

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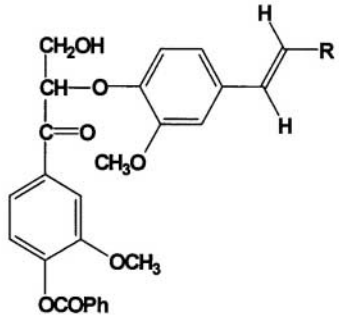

6a R = CH_3
b R = CHO

nals for **2** and **3** correspond closely to those of the synthetic neolignans **4** and **5**.

The correspondence of the ^{1}H NMR data of the neolignan mixture to that of the *erythro* isomer **4** is explicable because the neolignan mixture of Luyengi *et al*. was estimated to be a 3:1 mixture of *erythro:threo* isomers [2], so that the signals assigned to the latter would be relatively minor. The ^{1}H NMR signals of the neolignan mixture could be reinterpreted in terms of the contribution of each isomer to the mixture (Table 1). The multiplet assigned to the 8′ proton at 6.23 ppm was in fact a mixture of two double triplets centred at 6.23 and 6.25 ppm for **4** and **5**, respectively, the double doublet at 6.67 ppm was a composite of two doublets for each isomer and the broad doublet at 6.76 ppm and triplet at 6.85 ppm were each comprised of two double doublets. It is well recognised that the chemical shifts of the hydroxyl protons are

Table 1. ^{1}H NMR chemical shifts of compounds in DMSO-d_6

H (**2** and **3**)*	**2** and **3***	**4**	**5**	H (**4** and **5**)
9 (2H)	3.58 (*bs*)	3.59 (*m*)	3.23 (*m*)	9a (1H)
		3.59 (*m*)	3.57 (*m*)	9b (1H)
9′ (2H)	4.08 (*bs*)	4.08 (*m*)	4.09 (*m*)	9′ (2H)
8 (1H)	4.29 (*m*)	4.30 (*m*)	4.26 (*m*)	8 (1H)
7 (1H)	4.68 (*m*)	4.70 (*m*)	4.71 (*m*)	7 (1H)
8′ (1H)	6.23 (*m*)	6.23 (*dt*) (15.9, 5.2)	6.25 (*dt*) (15.9, 5.2)	8′ (1H)
7′ (1H)	6.44 (*d*) (16.0)	6.43 (*bd*) (15.9)	6.45 (*bd*) (15.9)	7′ (1H)
5 (1H)	6.67 (*dd*) (8.0, 2.5)	6.67 (*d*) (8.0)	6.68 (*d*) (8.2)	5 (1H)
6 (1H)	6.76 (*bd*) (8.0)	6.77 (*dd*) (8.0, 1.6)	6.76 (*dd*) (8.2, 2.0)	6 (1H)
4′ (1H)	6.85 (*t*) (8.0)	6.84 (*dd*) (8.4, 1.8)	6.86 (*dd*) (8.4, 2.0)	6′ (1H)
5′ (1H)	6.92 (*d*) (8.0)	6.92 (*d*) (8.4)	6.94–6.98 (*m*)	5′ (1H)
2,3′ (2H)	6.98 (*m*)	6.99 (*m*)	6.94–6.98 (*m*)	2 or 2′ (1H)
		6.99 (*m*)	7.04 (*d*) (2.0)	2 or 2′ (1H)
OCH_3 (6H)	3.72 (*s*)	3.72 (*s*)	3.72 (*s*)	OCH_3
		3.73 (*s*)	3.79 (*s*)	OCH_3
9-OH	3.00 (*bm*)	4.62 (*t*) (5.4)	4.65 (*t*) (5.2)	9-OH
9′-OH	4.85 (*bs*)	4.81 (*t*) (5.4)	4.81 (*t*) (5.4)	9′-OH
7-OH	5.30 (*m*)	5.33 (*d*) (4.4)	5.28 (*d*) (4.4)	7-OH
Ar–OH		8.78 (*s*)	8.80 (*s*)	Ar–OH

*Data from Ref. [2].

dependent on the conditions under which the NMR experiments are conducted.

The ^{13}C NMR signals of the neolignan mixture **2** and **3** generally match those of isomers **4** and **5** (Table 2), although Luyengi *et al.* [2] reported an additional signal for C-5′ at 115.01 ppm in the spectrum of the mixture which did not correspond closely with a signal in either of the synthetic isomers [2]. No attempt was made to assign the ^{13}C NMR signals to the aromatic carbon atoms in **4** and **5** in the present work.

Because of the close correspondence of the ^{1}H and ^{13}C NMR data of the isomeric mixture and those of the synthetic neolignans **4** and **5**, it is clear that the structures **2** and **3** given by Luyengi *et al.* [2] to the isomeric neolignan mixture are incorrect and that these substances are the known neolignans **4** and **5**. Compounds **4** and **5** have been reported recently as components of hydrolysates from treatment of spruce (*Picea abies*) wood and high yield pulps derived from spruce wood with an aqueous solution at pH 4 [11]. A mixture of the dilignol isomers **4** and **5** was previously obtained by mild acid treatment of spruce wood [12]. One of the isomers (**4** or **5**) has been isolated as a neolignan extractive from the wood of *Larix leptolepis* [13] and both isomers have been found as components of the bark of *Ehretia ovalifolia* [14].

Table 2. ^{13}C NMR chemical shifts of compounds in DMSO-d_6

C (**2** and **3**)*	**2** and **3***	**4**	**5**	C (**4** and **5**)
OCH_3	55.41	55.3	55.3	OCH_3
OCH_3	55.57	55.4	55.5	OCH_3
9	60.07	60.0	60.0	9
9′	61.62	61.5	61.5	9′
7	70.88		70.8	7 (*threo*)
7	71.56	71.5		7 (*erythro*)
8	83.64	83.5		8 (*erythro*)
8	84.23		84.2	8 (*threo*)
3′	109.76	109.6	109.6	
2	111.35	111.2	110.8	
5	114.53	114.4	114.5	
5′	115.01			
5′	115.35	115.3	115.3	
4′	119.03	118.9	118.8	
6	119.46	119.3	118.9	
7′,8′	128.52	128.3	128.4	7′ or 8′
		128.4	128.4	7′ or 8′
1′	130.05	129.8	130.0	
1	132.89	133.1	132.8	
4	145.60	145.3	145.3	
3	146.91	146.8	146.8	
6′	147.78	147.4	147.7	
2′	149.65	149.5	149.5	

*Data from Ref. [2].

The use of NMR spectroscopy for structural determination of neolignans has led to several instances of incorrect assignments being reported [3, 15, 16]. It is thus recommended that complementary methods should be investigated in addition to the NMR measurements for structural determinations. Thus far, there is no evidence to support the existence of 8-*O*-6′-linked neolignans in nature.

EXPERIMENTAL

Spectra

^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100.6 MHz with a Varian XL-400 (VXR-5000) instrument. Chemical shifts are given in ppm from tetramethylsilane (δ 0.00).

1-*(*4-*Benzoyl*-3-*methoxyphenyl)*-3-*hydroxy*-2-*{*2-*methoxy*-4-*[(E)*-1-*propenyl]phenoxy}*-1-*propanone (**6a**)*

This was prepared starting from acetoguaiacone and (*E*)-isoeugenol according to methods applied to the preparation of 1-(4-benzoyl-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)-1-pro-

panone [17, 18] ^{1}H NMR ($CDCl_3$) δ 1.86 (3H, *dd*, J = 1.6, 6.6 Hz, H-9′), 3.07 (1H, *br t*, OH), 3.86 (6H, *s*, 2 × OCH_3), 4.09 (2H, *m*, H-9), 5.41 (1H, *dd*, J = 4.5, 5.6 Hz, H-8), 6.12 (1H, *qd*, J = 6.6, 15.7 Hz, H-8′), 6.32 (1H, *qd*, J = 1.6, 15.7 Hz, H-7′) and 6.7–8.3 (11H, *m*, Ar–H).

*1-(4-benzoyl-3-methoxyphenyl)-2-{4-[(E)-2-formylvinyl]-2-methoxyphenoxy}-3-hydroxy-1-propanone (**6b**)*

Compound **6a** (370 mg) was oxidised with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone using a modification [5] of a procedure used for the preparation of coniferaldehyde [6]. Adsorption of the reaction mixture on a column of silica gel and elution with dichloromethane–ethyl acetate 2:1 gave compound **6b** (270 mg) ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, *s*, OCH_3), 3.90 (3H, *s*, OCH_3), 4.17 (2H, *m*, H-9′), 5.60 (1H, *dd*, J = 3.8, 6.0 Hz, H-8), 6.61 (1H, *dd*, J = 7.7, 15.7 Hz, H-8′), 7.39 (1H, *d*, J = 15.7 Hz, H-7′), 6.80–8.30 (11H, *m*, Ar–H) and 9.66 (1H, *d*, J = 7.7 Hz, CHO).

*Erythro- and threo-1-(4-hydroxy-3-methoxyphenyl)-2-{4-[(E)-3-hydroxy-1-propenyl]-2-methoxyphenoxy}-1,3-propanediol (**4** and **5**)*

Sodium borohydride (150 mg) was added to a solution of the aldehyde **6b** (270 mg) in ethanol (12 ml) and the mixture was kept at 20°C for 16 h. Sodium hydroxide (0.4 M, 7 ml) was added to the reaction mixture and, after a further 2 h at 20°C, the reaction mixture was acidified with 1 M hydrochloric acid and extracted with chloroform. Evaporation of the extract gave an oil [230 mg, *erythro*:*threo* **4**:**5** was 2:1 (^{1}H NMR)], which after anion exchange chromatography and elution with 0.06 M potassium tetraborate in ethanol–water 1:4 [7, 19] gave, successively, the *threo* and *erythro* compounds **5** and **4** (53 and 96 mg), respectively. **4** Tetra-acetate, ^{1}H NMR ($CDCl_3$) δ 2.03 (3H, *s*, CH_3CO), 2.095 (3H, *s*, CH_3CO), 2.101 (3H, *s*, CH_3CO), 2.31 (3H, *s*, CH_3CO), 3.80 (3H, *s*, OCH_3), 3.82 (3H, *s*, OCH_3), 4.25 (1H, *dd*, J = 4.1, 12.0 Hz, H-9), 4.45 (1H, *dd*, J = 5.8, 12.0 Hz, H-9), 4.66 (1H, *m*, H-8), 4.71 (2H, *dd*, J = 1.0, 6.5 Hz, H-9′), 6.07 (1H, *d*, J = 5.3 Hz, H-7), 6.17 (1H, *dt*, J = 6.5, 15.9 Hz, H-8′), 6.57 (1H, *br d*, J = 15.9 Hz, H-7′) and 6.7–7.1 (6H, *m*, H–Ar). **5** Tetra-acetate ^{1}H NMR ($CDCl_3$) δ 2.00 (3H, *s*, CH_3CO), 2.05 (3H, *s*, CH_3CO), 2.10 (3H, *s*, CH_3CO), 2.31 (3H, *s*, CH_3CO), 3.82 (3H, *s*, OCH_3), 3.83 (3H, *s*, OCH_3), 4.06 (1H, *dd*, J = 5.8, 12.0 Hz, H-9), 4.30 (1H, *dd*, J = 4.6, 12.0 Hz, H-9), 4.63 (1H, *m*, H-8), 4.71 (2H, *d*, J = 6.7 Hz, H-9′), 6.11 (1H, *d*, J = 6.3 Hz, H-7), 6.18 (1H, *dt*, J = 6.7, 15.9 Hz, H-8′), 6.59 (1H, *br d*, J = 15.9 Hz, H-7′) and 6.8–7.1 (6H, *m*, H–Ar). Lit. [3, 11] identical NMR spectra for tetra-acetates of **4** and **5**.

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