Furanoid and Furofuranoid Lignans from Daphne oleoides

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Daphne oleoides, Thymeleceae, Furanoid and Furofuranoid Lignans

Furofuranoid lignan (1) and (2) and furanoid lignan (3) have been isolated from Daphne oleoides and their structures elucidated through chemical and spectroscopic studies as 2-(3'-methoxy-4'-O-α-D-galactopyranosylphenyl)-6-(3'-methoxy-4'-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (1), 2-(3',5'-dimethoxy-4'-O-α-D-galactopyranosylphenyl)-6-(3'-methoxy-4'-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (2), and 4,9'-dihydroxy-3,3'-dimethoxy-4'-O-β-D-glucopyranosyl-7,7'-epoxy lignan (3). Two known lignans (4) and (5) have also been reported for the first time from this species.

Introduction

Daphne oleoides L. (Thymeleceae) is a xerophytic shrub found in northern hilly regions of Pakistan. It finds a variety of uses in folk medicines [1]. A number of compounds have previously been reported from the chloroform soluble extract of this plant. Following further studies on the ethyl acetate soluble fraction of D. oleoides, it has been possible to isolate two new furofuranoid lignans 1 and 2, a furanoid lignan 3 and two known lignans 4 [2] and 5 [3] reported for the first time from this species.

Results and Discussion

Compound 1: The IR spectrum showed absorptions at 3510, 1645 and 1470 cm\(^{-1}\) characteristic for hydroxyl and aromatic moieties, respectively. The molecular formula of 1 was assigned as C\(_{26}\)H\(_{32}\)O\(_{11}\) through HR-MS (neg., FAB) showing the [M\(^+\)-H] peak at \(m/z\) 519.1920 (cald. for C\(_{26}\)H\(_{33}\)O\(_{11}\): 519.1919). The \(^{13}\)C NMR experiment revealed signals for four methylene, fourteen methine, two methyl and six quaternary carbons. The \(^1\)H NMR spectrum indicated the presence of two methoxy groups (\(\delta 3.81\) and \(3.83\)) and the signals between \(\delta 3.08\) and 4.70 indicated the presence of a furofuranoid moiety [4]. The compound 1 was, therefore, clearly a derivative of 2,6-diarylmethane-3,7-dioxabicyclo[3.3.0]octane. The C-1-C-5 bond of naturally occurring furofuranoid lignans is characteristic in the cis configuration, and the \(^1\)H NMR spectrum (Table I) indicated that this was true for 1. The aryl substituents of C-2 and C-6 can be either axial or equatorial, allowing for three types of stereoisomers. Compound 1 was concluded to be an equatorial-equatorial isomer on the basis of the following features of its \(^1\)H NMR spectrum [4,5]: (1) similar environment for methine protons 1-H and 5-H and hence the similar chemical shift at \(\delta 3.08\) (2H, m); (2) similar chemical shift of benzylic protons at \(\delta 4.70\) (2H, \(J = 5.0\) Hz); (3) the presence of two equatorial methylene protons at C-4 and C-8, respectively, found at \(\delta 4.18\)–4.28 due to the deshielding by the equatorial aromatic rings.

The presence of a carbohydrate moiety was evident from the \(^1\)H NMR (anomeric equatorial proton at \(\delta 4.72\), \(J = 2.0\) Hz) and \(^{13}\)C NMR spectrum (anomeric carbon at \(\delta 100.98\) and other oxygen bearing carbons at \(\delta 61.94, 68.41, 71.10, 71.80,\) and 72.60). A comparison of the signals for these carbons with those reported in the literature [6] revealed its identity as α-D-galactopyranoside, which was further confirmed by the comparative TLC of the sugar moiety with an authentic sample after the acid hydrolysis of compound 1.

The remaining problem was to locate the relative positions of various substituents in the two aromatic rings. The peak at \(m/z\) 151 in EI-MS was
Table I. $^1$H and $^{13}$C NMR data for compounds 1 and 2.

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<th>$^1$H NMR (HMQC) [δ/ppm]</th>
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due to known fragmentation of furofuranoid lignans [7], allowing us to assign one of the two methoxy and a hydroxy group to one of the aromatic ring and the remaining methoxy group to the other. The signals in the aromatic region of the $^1$H NMR spectrum at δ 7.07 (1H, d, J = 8.23 Hz), 7.00 (1H, d, J = 8.10 Hz), 6.96 (1H, d, J = 1.7 Hz), 6.90 (1H, d, J = 1.8 Hz), 6.86 (1H, dd, J = 1.7, 8.23 Hz) and 6.81 (1H, dd, J = 1.8, 8.10 Hz) were due to 5'-H, 5''-H, 2'-H, 2''-H, 6'-H, and 6''-H, respectively, revealing the 3', 4' and 3'', 4'' substitution pattern in the aryl groups. The positions of various groups in the aromatic rings were further confirmed by an HMBC experiment. The anomic proton of the sugar moiety at δ 4.72 showed the $^3$J interactions with C-4' at δ 146.6, while another $^3$J interaction was observed between methoxy protons at δ 3.83 and C-3' at δ 149.2. The protons at δ 3.81 showed $^3$J interaction with C-3' at δ 147.2 and of C-4' at δ 145.4 with 2''-H (δ 6.90) and 6''-H (δ 6.81), confirming the presence of methoxy and hydroxy groups at C-3'' and C-4'', respectively. Other HMBC interactions were in complete agreement to the proposed structure of 1 as 2-(3'-methoxy-4'-O-α-D-galactopyranosylphenyl)-6-(3''-methoxy-4''-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane.

Compound 2: The molecular formula of 2 was assigned as C$_{27}$H$_{34}$O$_{12}$ through HR-MS (neg., FAB) showing the [M$^+$H] peak at m/z 549.1997 (calcd. for C$_{27}$H$_{34}$O$_{12}$: 549.1988.) The IR, $^1$H and $^{13}$C NMR spectra were very similar to 1. The molecular formula of 2 indicated the presence of an additional methoxy group. This group was assigned to C-5' as protons at C-2' and C-6' were observed together at δ 6.54 in the $^1$H NMR spectrum. Further confirmation was obtained by an HMBC experiment which showed $^3$J interactions of C-5' (δ 149.9) with protons 2'-H and 6'-H. The structure of 2 was, therefore, assigned as 2-(3',5'-dimethoxy-4'-O-α-D-galactopyranosylphenyl)-6-(3''-methoxy-4''-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane. The $^1$H, $^{13}$C and HMBC data are given in Table I to reveal the close similarities between 1 and 2.

Compound 3: The molecular formula of 3 was assigned as C$_{26}$H$_{34}$O$_{11}$ by HR-MS (neg., FAB),
showing the molecular ion peak [M+-H] at m/z 521.2088 (calcd. for C_{2a}H_{33}O_{11}: 521.2079). The IR spectrum of compound 3 showed absorptions at 3510, 1640 and 1470 cm\(^{-1}\), characteristic for a hydroxy and aromatic moieties, respectively. Methylation of 3 with diazomethane yielded 3a with an additional methoxy group, indicating the presence of a phenolic group in 3.

The \(^1\)H NMR spectrum of 3 displayed the presence of six aromatic protons in a complicated pattern at \(\delta\) 7.10, 6.88, 6.77, 6.73, 6.65, and 6.56, respectively, two methoxy groups at \(\delta\) 3.73 and 3.74 (each 3H, s). The remaining protons were found between \(\delta\) 2.41 and 4.96. The DEPT experiment revealed the signals of fourteen methine, four methylene and two methyl carbon atoms. The quaternary atoms were determined by subtracting these from the broad band spectrum. Both \(^1\)H and \(^{13}\)C NMR spectra indicated the presence of a sugar moiety (anomeric proton at \(\delta\) 4.84, \(J = 7.4\) Hz, and anomeric carbon at \(\delta\) 100.42 in addition to other oxygen bearing carbons at \(\delta\) 60.8, 69.6, 71.9, 76.9 and 77.0).

Acid hydrolysis of 3 provided 3b and sugar moiety; the latter was identified as \(\beta\)-D-glucose by retention time of its trimethylsilyl ether in gas chromatography [8]. The \(\beta\) configuration was further confirmed by the coupling constant of the anomeric proton (\(J = 7.4\) Hz).

Acetylation of 3 with acetic anhydride and pyridine gave a hexaacetate 3c revealing the six hydroxy groups. Five of these have already been accounted by sugar and phenolic moieties, the remaining one was shown to be a primary hydroxy group through \(^1\)H NMR (dd at \(\delta\) 4.20 and 3.74, 1H each). It was confirmed by comparing the \(^1\)H NMR data of 3 and 3c, the latter showing a downfield shift of these protons at \(\delta = 4.55\) and 4.02, respectively.

Treatment of aglycone 3b with diazomethane gave the tetramethyl ether 3d. As only one phenolic group has been inferred in 3, the additional phenolic group in 3d must arise by loss of a glucose moiety confirming the phenolic O-linkage.

The \(^{13}\)C NMR spectrum was very similar to those of laracinal and daphnelignan, respectively, showing similarities in stereochemistry of these compounds. It was also confirmed by similarities in fragmentation pattern in EI-MS spectrum showing characteristic fragments at m/z 137 and 123. The fragment at m/z 137 was also found for daphnelignan and allowed us to assign the methoxy and hydroxy moieties at C-3‘ and C-4’, respectively.

The presence of the remaining methoxy group and the sugar moiety at C-3” and C-4”, respectively, was confirmed on the basis of an HMBC experiment. The proton at \(\delta\) 7.1 (5’-H) showed cross peaks to carbons at \(\delta\) 148.9 (C-4’), 137.7 (C-1’) and 110.3 (C-2’). Likewise proton 6’-H (\(\delta\) 6.77) showed connectivities to carbons at \(\delta\) 148.9 (C-4’) and 137.7 (C-1’). Other important cross peaks were found between proton 5-H (\(\delta\) 6.65) and carbons at \(\delta\) 145.6 (C-5), 144.6 (C-4) and 131.1 (C-1), proton 7-H (\(\delta\) 2.80) and carbons at \(\delta\) 131.1 (C-1), 41.9 (C-8) and proton \(\delta\) 4.96 (7’-H) with carbons at \(\delta\) 52.4 (C-8’) and 137.7 (C-1’). The configurations of the chiral centres were confirmed by NOE difference measurements. Irradiation of a proton at \(\delta\) 2.80 (8-H) caused an enhancement of the signal at \(\delta\) 2.56 (8’-H) and similarly 7’-H showed NOE interactions with 7-H and 9’-H. Irradiation of the signal at \(\delta\) 4.84 (anomeric proton) caused an enhancement of the peak coupled with an ortho proton at \(\delta\) 7.1 (5’-H), confirming the position of glucose linkage at C-4’ which was further confirmed by HMBC interactions. Biogenetic evidence was provided by co-occurrence of larciresinol, in the same plant. The structure of 3 was, therefore, assigned as the tetrahydrofuran derivative 4,9’-dihydroxy-3’,3-dimethoxy-4’-O-8-D-glucopyranosyl-7’-9-epoxylignan.

**Experimental Section**

**General experimental procedures:** IR spectra of all the compounds were measured on a Schimadzu Infrared spectrophotometer IR 460. EI mass spectra were recorded on a Varian MAT 311, FAB-MS measurements were done on a JEOL-HX 110 mass spectrometer using glycerol as internal standard. NMR experiments were carried out on a Bruker AMX-400 instrument (\(^1\)H: 400.1 MHz; \(^{13}\)C: 100.61 MHz). DEPT experiments were carried out with pulse angles \(\theta = 45^\circ, 90^\circ, 135^\circ\). Chemical shifts are in \(\delta\) with TMS as internal standard and coupling constants are in Hz. Pyridine-\(d_5\) was used as solvent in all NMR experiments of compounds 3, 4 and 5 whereas CDCl\(_3\) with a few drops of CD\(_3\)OD was used as solvent in case of compound 1 and 2. 2D experiments were done on a Bruker AMX-500 instrument. Silica gel 60 (35–70 mesh) was used for column chromatography. TLC was carried out on a precoated Kieselgel 60,
F$_{254}$ aluminum sheet (Merck) using a CHCl$_3$/MeOH mixture 89:11 for compounds 4, 5 and 85:15 in case of 1, 2 and 3); spots were visualized by spraying with a solution of ceric sulphate in 10% H$_2$SO$_4$.

Collection of plant material, extraction and isolation: Whole plant material of D. oleoides was collected from Mansehra district of North West Frontier Province, Pakistan, and was identified by Prof. Iftikhar Hussain Shah of Faculty of Pharmacy, Gomal University, D. I. Khan, Pakistan, in Feb. 1995 where a voucher specimen (DIU-2119x) has been deposited in the Herbarium.

Shade dried ground whole plant material (15 kg) of D. oleoides was extracted thrice with methanol. The combined methanolic extract was evaporated under reduced pressure and to the resulting gummy residue was added H$_2$O and the mixture was successively extracted with hexane, chloroform, ethyl acetate and n-butanol. The ethyl acetate extract was subjected to column chromatography using hexane-chloroform and chloroform-methanol gradient systems to obtain fractions (A-M). The fraction E obtained from chloroform-methanol (98:2) was subjected to column chromatography eluting with chloroform-ethyl acetate and the residue recovered from the cold. The XH NMR (500 M Hz, pyridine-d$_5$) showed an additional resonance at $\delta$ 3.67 (3H, s, OCH$_3$). - HR-MS (neg., FAB): $m/z$ = 519.2088 [M$^+$-H] (calcd. for C$_{26}$H$_{31}$O$_n$: 521.2088). - MS (EI, 70 eV): $m/z$ (%) = 358 (48.2) [M$^+$-sugar moiety], 205 (22.3), 196 (10.2), 190 (11.2), 180 (11.6), 163 (30.6), 162 (9.5), 152 (23.5), 151 (100) 150 (30.5), 137 (46.67), 133 (9.6), 131 (8.29).

Hydrolysis of 1: A solution of compound 1 (8 mg) in methanol (1 ml) and 1N HCl (1 ml) was refluxed for 4h. The solution was concentrated under reduced pressure and diluted with H$_2$O (5 ml). It was extracted with ethyl acetate. The sugar in the aqueous phase was identified as galactose by comparative TLC with an authentic sample using solvent system n-BuOH/EtOAc/i-PrOH/HOAc/H$_2$O (7:20:12:7:6). The TLC was run thrice in the same direction and spots were visualized with aniline phosphate reagent. The sugar was found to be D-galactose.

Compound 2: IR (KBr): $\nu$ = 3520, 1650 and 1478 cm$^{-1}$. - $^1$H and $^{13}$C NMR data are given in Table I. - HR-MS (neg., FAB). $m/z$ = 549.1998 [M$^+$], (calcd. for C$_{27}$H$_{33}$O$_2$: 549.1997). - MS (EI, 70 eV): $m/z$ (%) = 388 (100) [M$^+$-sugar moiety], 210 (11), 193 (12), 183 (15), 180 (14), 163 (18), 155 (23), 154 (68), 153 (47), 151 (45), 124 (24), 123 (30).

Acid hydrolysis and the identification of the sugar part were done by the procedure described for 1, and the sugar was identified as D-galactose.

Compound 3: IR (KBr): $\nu$ = 3510, 1640 and 1470 cm$^{-1}$. - $^1$H NMR and $^{13}$C NMR data is given in Table II. - MS (EI, 70 eV): $m/z$ (%) = 360 (100) [M$^+$-sugar moiety], 236 (17), 194 (27), 137 (80), 123 (8), 66 (24).

Compound 3a: To an ethereal solution of 3 (12 mg), freshly prepared CH$_2$N$_2$ was added in excess and the solution was kept at rt overnight. Usual workup of the reaction mixture afforded 3a, which precipitated as an amorphous powder on keeping its concentrated methanolic solution in the cold. The $^1$H NMR (500 MHz, pyridine-d$_5$) showed an additional resonance at $\delta$ 3.69 (3H, s, OCH$_3$). - HR-MS (neg., FAB): $m/z$ = 535.2248 [M$^+$-H] (calcd. for C$_{27}$H$_{33}$O$_{11}$: 535.2239).

Compound 3b: A solution of 3 (16 mg) in MeOH (5 ml) containing 1N HCl (4 ml) was refluxed for 4h, concentrated under reduced pressure and diluted with H$_2$O (5 ml). It was extracted with ethyl acetate and the residue recovered from Table II. $^1$H and $^{13}$C NMR data of compound 3.

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<tr>
<td>2'</td>
<td>CH</td>
<td>110.3</td>
<td>6.73 (d, J = 1.8 Hz)</td>
</tr>
<tr>
<td>3'</td>
<td>C</td>
<td>147.4</td>
<td>–</td>
</tr>
<tr>
<td>4'</td>
<td>C</td>
<td>148.9</td>
<td>–</td>
</tr>
<tr>
<td>5'</td>
<td>CH</td>
<td>112.8</td>
<td>7.1 (d, J = 8.4 Hz)</td>
</tr>
<tr>
<td>6'</td>
<td>CH</td>
<td>115.2</td>
<td>6.77 (dd, J = 8.4, 1.8 Hz)</td>
</tr>
<tr>
<td>7'</td>
<td>CH</td>
<td>81.6</td>
<td>4.96 (d, J = 7.0 Hz)</td>
</tr>
<tr>
<td>8'</td>
<td>CH$_2$</td>
<td>52.4</td>
<td>2.56 (m)</td>
</tr>
<tr>
<td>9'</td>
<td>CH$_2$</td>
<td>58.6</td>
<td>4.20 (dd, J = 11.5, 7.1 Hz)</td>
</tr>
<tr>
<td>10'</td>
<td>CH$_2$</td>
<td>58.6</td>
<td>3.74 (dd, J = 11.5, 4.2 Hz)</td>
</tr>
<tr>
<td>11'</td>
<td>CH</td>
<td>100.42</td>
<td>4.84 (d, J = 7.4 Hz)</td>
</tr>
<tr>
<td>2'</td>
<td>CH</td>
<td>71.9</td>
<td>3.15 (m)</td>
</tr>
<tr>
<td>3'</td>
<td>CH</td>
<td>76.9</td>
<td>3.22 (m)</td>
</tr>
<tr>
<td>4'</td>
<td>CH</td>
<td>69.6</td>
<td>3.54 (m)</td>
</tr>
<tr>
<td>5'</td>
<td>CH</td>
<td>77.0</td>
<td>3.45 (m)</td>
</tr>
<tr>
<td>6'</td>
<td>CH</td>
<td>60.8</td>
<td>3.81 (m)</td>
</tr>
</tbody>
</table>

OMe x 2
| CH$_3$       | 55.6, 55.8  | 3.73, 3.74 (each for 3H, s) |
the organic phase was subjected to preparative TLC to obtain compound 3b which was identified as the corresponding aglycone of 3. The $^1$H NMR (500 MHz, pyridine-d$_5$) of compound 3b showed similar resonances as 3, except for the now absent signals of the sugar moiety. – HR-MS (neg., FAB): $m/z = 359.1542$ [M$^+\text{-H}$] (calcd. for C$_{20}$H$_{23}$O$_6$: 359.1494).

**Compound 3c:** A mixture of 3 (4 mg), Ac$_2$O (6 ml) and pyridine (7 ml) was stirred overnight at rt and worked up in the usual way to afford 3c. The $^1$H NMR spectrum (500 MHz, pyridine-d$_5$) showed, in relation to 3, additional resonances at $\delta$ 2.21 (3H, s, 4-OOCMc), 2.15 (3H, s, 9'-OOCMc), 2.02 (12H, s, 4$\times$OOCMc, sugar). – HR-MS (neg., FAB): $m/z = 773.2742$ [M$^+\text{-H}$] (calcd. for C$_{38}$H$_{45}$O$_{17}$: 773.2734).

**Compound 3d:** Methylation of 3b as described for 3 afforded compound 3d. The $^1$H NMR spectrum (500 MHz, pyridine-d$_5$) showed in relation to 3b, an additional resonance at $\delta$ 3.75 (6H, s, 2xOMe). – HR-MS (neg., FAB): $m/z = 387.1863$ [M$^+\text{-H}$] (calcd. for C$_{22}$H$_{27}$O$_6$: 387.1854).

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