

## Four New Furans from the Roots of *Ligularia przewalskii*

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FOUR NEW FURANS FROM THE ROOTS  
OF *LIGULARIA PRZEWALSKII*

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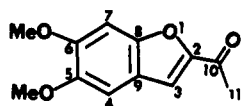
ABSTRACT.—A phytochemical investigation of the roots of *Ligularia przewalskii* afforded ten compounds including four new furans (two tremetone derivatives, one benzofuran derivative and one naphthofuran eremophilane derivative). Their structures were elucidated by high-field nmr spectroscopy and chemical transformations.

Several new eremophilanolides and other constituents from the genus *Ligularia* (Compositae) have been reported in our previous work (1–5). Recently, we have investigated *Ligularia przewalskii* (Maxim.) Diels, which is common in northwestern China and has been used in folk medicine since ancient times (6), and have found it to contain several furans. This paper describes the isolation and structural elucidation of the new compounds 1–4.

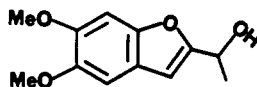
The petroleum ether-Et<sub>2</sub>O-Me<sub>2</sub>CO (1:1:1) extract of the dried and powdered roots of *L. przewalskii* was subjected to column chromatography over Si gel and fractionated, as described in the Experi-

mental section, to yield  $\beta$ -sitosterol, euparin (7), *p*-hydroxybenzaldehyde, 2-hydroxyplatyphyllid (8), platyphyllid (9), and *p*-hydroxycinnamic acid methyl ester, as well as the four new compounds 2-acetyl-5,6-dimethoxybenzofuran [1], 2-isopropenyl-5-acetyl-7-hydroxy-2,3-dihydrobenzofuran [2], 5-acetyl-7-methoxybenzofuran [3] and 1,3-dimethoxy-4,6,11-trimethylnaphthofuran [4].

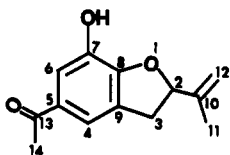
Compound 1 was obtained as yellowish needles upon recrystallization from CHCl<sub>3</sub>. The <sup>1</sup>H-nmr spectrum of 1 exhibited six singlets, three of which were aromatic protons appearing at  $\delta$  7.41, 7.04, and 7.03 (each 1H). The other three were all Me singlets. Two were MeO



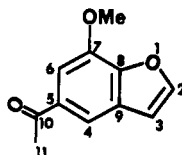
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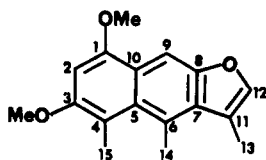
1a



2



3



4

signals at  $\delta$  3.92 and 3.94, while the other was due to an acetyl group at  $\delta$  2.55 associated with the  $^{13}\text{C}$ -nmr resonances at  $\delta$  187.6 (CO) and 26.1 ( $\text{CH}_3$ ) (Tables 1 and 2). Coupled with the  $^{13}\text{C}$ -nmr and ir spectra (see Experimental), the presence of a benzofuran ring moiety could be easily deduced. Two of the three protons were located on the benzene ring with a para relationship, while the other had to be assigned to the furan ring. Almost all of these naturally occurring derivatives have a substituent at C-2 (10,11), so this furan-ring proton was most likely at H-3. The  $^{13}\text{C}$ -nmr spectrum exhibited a methine carbon of the furan ring, which appeared upfield at  $\delta$  95.1 (CH), while another quaternary carbon also due to this furan ring occurred as a lowfield signal [ $\delta$  147.8 (C)]; this provided further evidence that the substituent was

indeed at C-2 and not C-3 in the furan ring. Thus, a 2,5,6-trisubstituted pattern of the benzofuran skeleton was concluded in the case of **1**.

The sole remaining structural problem was the location of the acetyl group; it has been observed that many benzofuran derivatives previously isolated from *Ligularia* species have a 5-acetyl group (e.g., euparin and tremetone) (10,11). However, this possibility could be eliminated by the fact that the  $^{13}\text{C}$ -nmr spectrum of **1** showed no carbon resonances due to an acetyl group attached to the benzene ring, which should normally appear at  $\delta$  130–140 (aromatic carbon) and  $\delta$  194–200 (keto group) (12). Furthermore, reduction of **1** gave **1a**. In the  $^1\text{H}$ -nmr spectrum of **1a**, the previous acetyl Me singlet was changed to a doublet at  $\delta$  1.61 ( $J=6.6$  Hz) and a corre-

TABLE 1.  $^1\text{H}$ -Nmr Data of Compounds **1**, **1a**, and **2-4**.<sup>a</sup>

Proton	Compound				
	<b>1</b>	<b>1a</b>	<b>2</b>	<b>3</b>	<b>4</b> <sup>b</sup>
2	—	—	5.34 br dd (8.2, 9.3)	7.70 d (2.0)	7.10 s
3	7.41 s	6.50 br s	3.42 dd (8.2, 15.8)	6.86 d (2.0)	—
4	7.04 s	6.96 s	3.13 dd (9.3, 15.8)	7.86 d (1.2)	—
6	—	—	7.44 d (2.0)	7.49 d (1.2)	—
7	7.03 s	7.01 s	—	—	—
9	—	—	—	—	7.64 s
10	—	4.97 br q (6.6)	—	—	—
11	2.55 s	1.61 d (6.6)	1.78 br s	2.67 s	—
12	—	—	5.00 br s	—	7.37 br s
13	—	—	5.11 br s	—	2.50 br s
14	—	—	2.55 s	—	2.76 s
15	—	—	—	—	2.62 s
OMe	3.94 s	3.90 s	—	4.06 s	4.09 s
	3.92 s	3.90 s	—	—	4.11 s
Ar-OH	—	—	6.45 br s	—	—

<sup>a</sup>Recorded at 400 MHz in  $\text{CHCl}_3$ . For stated multiplicities,  $J$  values (Hz) are provided in parentheses.

<sup>b</sup>Measured by Bruker AC 80 FT-nmr spectrometer.

TABLE 2.  $^{13}\text{C}$ -Nmr Data of Compounds **1** and **3**.<sup>a</sup>

Carbon	Compound			
	<b>1</b>	DEPT	<b>3</b>	DEPT
C-2 .....	147.8	C	146.2	CH
C-3 .....	95.1	CH	105.6	CH
C-4 .....	113.7	CH	116.0	CH
C-5 .....	151.4	C <sup>b</sup>	133.9	C
C-6 .....	151.7	C <sup>b</sup>	107.6	CH
C-7 .....	102.9	CH	146.0	C <sup>b</sup>
C-8 .....	152.4	C	147.3	C <sup>b</sup>
C-9 .....	119.1	C	128.7	C
C-10 .....	187.6	C	197.5	C
C-11 .....	26.1	CH <sub>3</sub>	26.6	CH <sub>3</sub>
OMe .....	56.3	CH <sub>3</sub>	56.2	CH <sub>3</sub>
	56.3	CH <sub>3</sub>		

<sup>a</sup>Recorded at 100.16 MHz in CDCl<sub>3</sub>.<sup>b</sup>Assignments may be interchanged.

sponding quartet at  $\delta$  4.97 (br q,  $J=6.6$  Hz). Moreover, the previous lowfield proton at  $\delta$  7.41 (s, 1H), attached to the furan ring, was shifted remarkably upfield to  $\delta$  6.50 (brs, 1H) (ca. 0.91 ppm). This result disclosed that the acetyl group of **1** was most likely linked at C-2. After reduction, the acetyl group was converted to a hydroxyethyl group, and the H-3 lost the deshielding effect from the conjugated keto group and was shifted upfield as well as being broadened by H-10 of **1a**. The eims spectrum of **1** showed an  $[\text{M}]^+$  at  $m/z$  220. Together with the  $^{13}\text{C}$ -nmr data and the elemental analysis, the molecular formula of **1** was established as C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>, in accordance with the proposed structure. This compound has been reported as a synthetic product (13), but it has not been previously found as a natural product.

The structure of compound **2** clearly followed from the  $^1\text{H}$ -nmr data (Table 1), which were closely similar to those of 7-methoxytremetone, previously reported by Bohlmann *et al.* from *Helianthella uniflora* (14). However, in the  $^1\text{H}$ -nmr spectrum of compound **2**, the MeO signal was absent and was replaced by an OH singlet at  $\delta$  6.50 (br, 1H, disappeared after D<sub>2</sub>O exchange), in accordance with the corresponding absorption band at 3300 cm<sup>-1</sup> in the ir spectrum.

Furthermore, the fact that **2** showed a positive reaction in the FeCl<sub>3</sub>/EtOH test identified this OH as phenolic. Eims gave a molecular ion at  $m/z$  218, 14 mass units lower than that of 7-methoxytremetone, indicating **2** was a demethyl derivative of 7-methoxytremetone. Moreover, the fact that the chemical shifts of H-2 and H-3 as well as their coupling constants were all coincident with those of 7-methoxytremetone in the published report (14) also supported the proposed structure.

The  $^1\text{H}$ -nmr spectrum of compound **3** showed an uncomplicated pattern. A Me singlet appeared at  $\delta$  2.67 accompanied by a  $^{13}\text{C}$ -resonance at  $\delta$  26.6 as well as a ketone signal at  $\delta$  197.5. These signals suggested an acetyl group that was most likely attached to an aromatic ring. Furthermore, a MeO singlet was present and could be observed at  $\delta$  4.04, while the other two aromatic protons appeared at  $\delta$  7.86 and 7.49 as doublets ( $J=1.2$  Hz) and suggested that **3** was another tremetone derivative. However, there were no protons due to an isopropenyl group as commonly found at C-2, but two doublets with a small coupling constant ( $J=2.0$  Hz) at  $\delta$  6.86 and 7.70 (Table 1) could be observed. Because the latter two resonances were probably due to a pair of vicinal protons associated with

a furan ring, the presence of a nor-tremetone derivative with a benzofuran skeleton was suggested.

The eims data further supported the deduction by a peak at  $m/z$  190 consistent with the molecular formula,  $C_{11}H_{10}O_3$  (as were the results of elemental analysis as well as the  $^{13}C$ - and DEPT nmr data). The  $^{13}C$ -nmr spectrum of **3** was consistent with the proposed structure (Table 2). Biogenetically, **3** was most likely formed by the oxidation of methoxyeuparin and loss of the isopropenyl group.

The eims data of compound **4** showed a molecular ion at  $m/z$  270. Together with the elemental analyses, the molecular formula,  $C_{17}H_{18}O_3$ , could be deduced. The  $^1H$ -nmr spectrum of compound **4** exhibited three high-field Me singlets at  $\delta$  2.50, 2.62 and 2.76, as well as two Me singlets at  $\delta$  4.09 and 4.11 (each 3H) (Table 1), which suggested a naphthofuran-type eremophilane derivative. Apart from the broadened singlet at  $\delta$  7.37 (1H) due to the furan ring proton, two other lowfield protons appeared at  $\delta$  7.64 and 7.10 (each 1H) as singlets. Because the ir spectrum of **4** showed no phenolic OH group and **4** could not be acetylated, the two protons were both aromatic. Naphthofuran eremophilane derivatives usually have an OR substituent at C-3, not C-2 (15,16); thus the two aromatic protons were most likely at C-2 and C-9, with the two MeO groups at C-1 and C-3 because all the protons appeared as singlets.

## EXPERIMENTAL

**GENERAL EXPERIMENTAL PROCEDURES.**—Mps were determined on a Kofler hot-stage instrument and are uncorrected.  $^1H$ - and  $^{13}C$ -nmr spectra were measured on a Bruker AM400 FT-nmr spectrometer or a Bruker AC 80 FT-nmr spectrometer with TMS as internal reference. Ir spectra were recorded on a 5DX-FTIR spectrometer. Eims spectra were obtained on a VG ZAB-HS spectrometer at 70 ev.

**PLANT MATERIAL.**—The roots of *L. przewalskii* were collected in Zhang County, Gansu Province, People's Republic of China. A voucher specimen was identified by Prof. R. N.

Zhao and is deposited in the Herbarium of the Department of Pharmacy, Lanzhou Medical College.

**EXTRACTION AND ISOLATION.**—The air-dried roots of *L. przewalskii* (7.5 kg) were powdered and extracted with petroleum ether (60–90°)- $Et_2O$ - $Me_2CO$  (1:1:1) three times (3 days each) at room temperature. The resultant extract (135 g), which was subjected to cc over 1400 g Si gel with a petroleum ether/ $Et_2O$  gradient, was separated into four crude fractions (fractions 1–4). Fraction 1 was further separated by cc over Si gel with a petroleum ether/ $Me_2CO$  (100:1–10:1) gradient and was purified by prep. tlc using a petroleum ether/ $CH_2Cl_2$ / $Et_2O$  system, and finally gave 100 mg of euparin and 10 mg of **3**; fraction 2 was rechromatographed also with petroleum ether- $Me_2CO$  (50:1–5:1) followed by prep. tlc with petroleum ether/ $CH_2Cl_2$ / $Et_2O$  systems to afford 14 mg of **4**, 28 mg of platyphyllid, and 40 mg of compound **1**. By cc and prep. tlc separation with the same solvent systems as mentioned above, fraction 3 was found to contain 508 mg of  $\beta$ -sitosterol and 15 mg of *p*-hydroxycinnamic acid methyl ester. Fraction 4, when subjected to further cc (Si gel) with  $CHCl_3$ - $Me_2CO$  (1:0–1:1) followed by repeated prep. tlc, finally afforded 12 mg of **2**, 50 mg of *p*-hydroxybenzaldehyde, and 45 mg of 2-hydroxyplatyphyllid.

The known compounds were identified by comparing their corresponding properties (mps, ms, ir and  $^1H$ -nmr) with literature values, and some were directly compared with authentic samples.

**2-Acetyl-5,6-dimethoxybenzofuran [1].**—Yellowish needles, mp 115–116° ( $CHCl_3$ ); *anal.* found C 65.46, H 5.48, calcd for  $C_{12}H_{12}O_4$ , C 65.45, H 5.45; ir  $\nu$  max (KBr) 3118, 3087, 1670 (C=O), 1620, 1545, 1490, 1439, 1295, 1213, 851 and 542  $cm^{-1}$ ;  $^1H$ - and  $^{13}C$ -nmr spectra, see Tables 1 and 2, respectively; eims  $m/z$  [ $M$ ] $^+$  220 (100), [ $M$ -Me] $^+$  205 (46), 177 (14), 135 (12), 119 (15), 77 (9), 63 (11), 43 (48).

**$NaBH_4$  reduction of 1.**—A solution of 20 mg of **1** in 3 ml MeOH was reduced with 14 mg  $NaBH_4$  by stirring for 30 min at room temperature diluting with 2M HCl, and extracting with  $Et_2O$ . The washed and dried extract was evaporated, and the residue (18 mg) was purified by prep. tlc [ $C_6H_6$ - $Et_2O$  (6:1)] to afford 12 mg of **1a**;  $^1H$ -nmr, see Table 1; ir  $\nu$  max (KBr) 3630 (OH), 3068, 1614, 1540, 1465, 1074, 965, 850, 545  $cm^{-1}$ .

**2-Propenyl-5-acetyl-7-hydroxy-2,3-dihydrobenzofuran (7-hydroxytremetone) [2].**—Colorless needles (recrystallized from  $CHCl_3$ ); mp 151–152°; *anal.* found C 71.58, H 6.43; calcd for  $C_{13}H_{14}O_3$ , C 71.56, H 6.42; ir  $\nu$  max (KBr) 3300 (OH), 1667 (Ph-C=O), 1600, 1491, 1333, 1364, 905 and 553

$\text{cm}^{-1}$ ;  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra, see Tables 1 and 2, respectively; eims  $m/z$   $[\text{M}]^+$  218 (96),  $[\text{M}-\text{Me}]^+$  203 (100), 175 (22), 157 (84), 129 (58), 115 (9), 91 (14), 77 (18), 43 (100).

*5-Acetyl-7-methoxybenzofuran* [3].—Colorless needles (recrystallized from  $\text{CHCl}_3$ ); mp 86–87°; *anal.* found C 69.47, H 5.25, calcd for  $\text{C}_{11}\text{H}_{10}\text{O}_3$ , C 69.47, H 5.26; ir  $\nu$  max (KBr) 3087, 3004, 1679, 1617, 1595, 1470, 1201, 1028  $\text{cm}^{-1}$ ;  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra, see Tables 1 and 2, respectively; eims  $m/z$   $[\text{M}]^+$  190 (66),  $[\text{M}-\text{Me}]^+$  175 (100),  $[\text{175}-\text{CO}]^+$  147 (62), 132 (10), 99 (12), 91 (10), 89 (15), 76 (18), 57 (18), 43 (45).

*1,3-Dimethoxy-4,6,11-trimethylnaphthofuran* [4].—Colorless needles (recrystallized from  $\text{CHCl}_3$ ); mp 156–157°; *anal.* found C 75.54, H 6.66, calcd for  $\text{C}_{17}\text{H}_{18}\text{O}_3$ , C 75.56, H 6.67; ir  $\nu$  max (KBr) 1614, 1503, 1471, 1203, 1116 and 832  $\text{cm}^{-1}$ ;  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra, see Tables 1 and 2, respectively; eims  $m/z$   $[\text{M}]^+$  270 (100),  $[\text{M}-\text{Me}]^+$  255 (52), 241 (6), 227 (20),  $[\text{227}-\text{Me}]^+$  212 (59), 184 (14), 167 (10), 135 (24), 106 (9), 91 (8), 76 (9).

#### ACKNOWLEDGMENTS

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