The Revised Structure of a Dihydrobenzofuran Derivative Isolated from *Lasiolaena morii*

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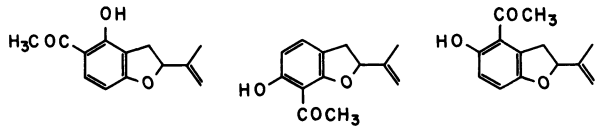
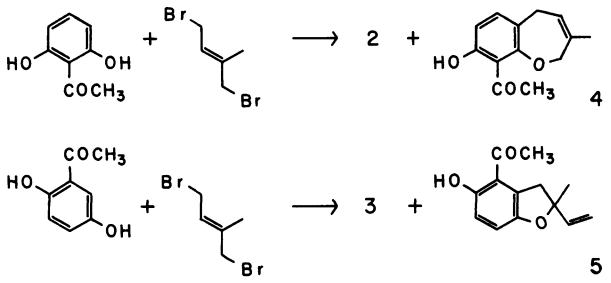
Synopsis. Two isopropenyldihydrobenzofuran derivatives are synthesized. By the comparison of ^{1}H NMR spectra, the proposed structure of a natural dihydrobenzofuran is revised to 4-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-5-ol.

In 1982, F. Bohlmann et al. isolated a new dihydrobenzofuran from *Lasiolaena morii* and proposed a structure of 5-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (**1**).[1] We have already synthesized this compound by a demethylation of 5-acetyl-2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran.[2] However, our synthetic compound showed a different ^{1}H NMR spectrum from that of the natural one. In the ^{1}H NMR spectra, the synthetic sample showed aromatic proton signals at δ=6.4 and 7.6 ppm, while the natural sample showed the corresponding signals at δ=6.81 and 6.99 ppm (Table 1). This fact indicates that the natural compound has another structure. Since the spectrum of the natural compound showed an intramolecular hydrogen-bonding (δ_{OH}=12.16 ppm) and no aromatic proton deshielded by an acetyl group in its ortho position, two structures, 7-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-6-ol (**2**) and 4-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-5-ol (**3**), are possible. In this paper, we describe the synthesis of these two dihydrobenzofurans and the structural reversion of the natural compound isolated from *Lasiolaena morii*.



1 2 3

The compound **2** and **3** were synthesized by the procedure reported by F. Bigi et al.[3] After the similar treatment of 2′,6′-dihydroxyacetophenone with 1,4-dibromo-2-methyl-2-butene, **2** and 9-acetyl-3-methyl-2,5-dihydro-1-benzoxepin-8-ol (**4**)[4] were obtained as cyclized products. In this reaction, 1,4-bis(2-acetyl-3-hydroxyphenoxy)-2-methyl-2-butene was also isolated as non-cyclized product. Similarly, the treatment of 2′,5′-dihydroxyacetophenone with 1,4-dibromo-2-methyl-2-butene gave two dihydrobenzofurans, **3** and 4-acetyl-2-methyl-2-vinyl-2,3-dihydrobenzofuran-5-ol (**5**).



4

5

In the ^{1}H NMR spectra, two isopropenyldihydrobenzofuran derivatives **2** and **3** showed an ABX coupling pattern due to protons in the dihydrofuranring, and **5** showed signals due to a quarternary methyl and a vinyl proton. On the other hand, **4** gave another spectral mode of the oxepin ring part [a broad methyl singlet, a broad two-proton doublet (H-5), a broad two-proton singlet (H-2), and a broad one-proton triplet (H-4)], similar to those of some natural 3-methyl-2,5-dihydro-1-benzoxepin derivatives.[5]

In the cyclization of 2′,4′-dihydroxyacetophenone,[3] two 2-isopropenyl-2,3-dihydrobenzofurans, 5-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (major) and 5-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-6-ol (minor), were obtained. However, in a similar cyclization of 2′,5′-dihydroxyacetophenone, all isolated products were formed via the alkylation at C-6, and no products derived from the C-4 alkylation were isolated.

Table 1. ^{1}H NMR Spectral Data of Isopropenyldihydrobenzofuran Derivatives [δ (ppm) and J(Hz) in $CDCl_3$]

	-CH_3	-$COCH_3$	3-CH_2		=CH_2		2-CH	Ar-H		-OH
Natural Compound	1.80 (s)	2.59 (s)	3.29 (dd, J=8.5, 16.5)	3.63 (dd, J=9.5, 16.5)	4.95 (broad s)	5.11 (broad s)	5.19 (dd, J=8.5, 9.5)	6.81 (d, J=8.5)	6.99 (d, J=8.5)	12.16[a] (s)
1	1.8 (s)	2.6 (s)	3.0 (dd, J=8, 16)	3.3 (dd, J=10, 16)	4.9 (broad s)	5.1 (broad s)	5.3 (dd, J=8, 10)	6.4 (d, J=9)	7.6 (d, J=9)	12.7[b] (s)
2	1.8 (s)	2.7 (s)	3.0 (dd, J=8, 15)	3.3 (dd, J=9.5, 15)	5.0 (broad s)	5.1 (broad s)	5.3 (dd, J=8, 9.5)	6.4 (d, J=8)	7.3 (d, J=8)	12.6 (s)
3	1.8 (s)	2.6 (s)	3.3 (dd, J=8, 16)	3.6 (dd, J=10, 16)	5.0 (broad s)	5.1 (broad s)	5.2 (dd, J=8, 10)	6.8 (d, J=9)	7.0 (d, J=9)	12.2 (s)

a) The data of natural compound from *Lasiolaena morii* provided by Bohlmann et al.[1] b) The data of our synthetic sample prepared by demethylation of 5-acetyl-2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran.[2]

The ^{1}H NMR data of the three 2-isopropenyl-2,3-dihydrobenzofuran derivatives are summarized in Table 1. As shown in the table, the natural compound isolated from *Lasiolaena morii* was identical with 4-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-5-ol (**3**).

Experimental

The melting points were uncorrected. The IR spectra were measured on a Hitachi EPI-S2 spectrophotometer in KBr disks, and the UV spectra were taken on a Hitachi 220A spectrophotometer in ethanol. The ^{1}H NMR spectra were recorded on a JEOL JNM-MH-60 NMR spectrometer or Varian XL-200 FT NMR spectrometer in CCl_4 or $CDCl_3$ and the mass spectra were determined on a JEOL JMS-OISG-2 mass spectrometer.

Cyclization of 2′,6′-Dihydroxyacetophenone with 1,4-Dibromo-2-methyl-2-butene. A suspension of the sodium salts was prepared by mixing 2′,6′-dihydroxyacetophenone (2.04 g, 13.4 mmol) and sodium hydride (52% mineral oil dispersion, 1.26 g, 27.8 mmol) in refluxing dry toluene (80 mL), and cooled to room temperature. To the suspension, 1,4-dibromo-2-methyl-2-butene (3.20 g, 14.0 mmol) was added and the mixture was refluxed for 24 h with stirring. After cooling, the mixture was treated with 10% hydrochloric acid and the toluene layer was collected. The toluene layer was washed with a 10% sodium carbonate solution and then extracted with a 5% sodium hydroxide solution. The sodium hydroxide solution was acidified with 10% hydrochloric acid and extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate. After removing the ether, the oily residue was chromatographed on a silica-gel column to give two fractions as benzene eluents. One of the fractions (185 mg) showed three peaks (ratio **A**:**2**:**4**=1.4:4.1:1) in GLC. Pure samples of **2** and **4** were obtained after re-chromatography and recrystallization, but the component **A** could not be isolated as pure state.[6] From the other fraction (45 mg), 1,4-bis(2-acetyl-3-hydroxyphenoxy)-2-methyl-2-butene was isolated in pure crystals. The three compounds isolated showed the following data. **2**: mp 59—60 °C (from hexane); IR 1640 cm^{-1}; ^{1}H NMR cited in table 1; UV 230 (log ε 4.10), 268 (4.13), 356 nm (3.66); MS *m/z* 218 (M^+), 203, 185. Found: C, 71.78, H, 6.64%. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47%. **4**: mp 81—82 °C (from hexane); IR 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.6 (3H, broad s), 2.8 (3H, s), 3.3 (2H, broad d, J=6 Hz), 4.5 (2H, broad s), 5.7 (1H, broad t, J=6 Hz), 6.7 (1H, d, J=8 Hz), 7.2 (1H, d, J=8 Hz), 12.8 ppm (1H, s); UV 221 (log ε 4.10), 260 (3.93), 341 nm (3.40); MS *m/z* 218 (M^+), 203, 185. Found: C, 71.49, H, 6.45%. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47%. 1,4-Bis(2-acetyl-3-hydroxyphenoxy)-2-methyl-2-butene; mp 133—135 °C (from benzene); IR 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.9 (3H, s), 2.6 (3H, s), 2.7 (3H, s), 4.6 (2H, s), 4.7 (2H, d, J=7 Hz), 5.9 (1H, t, J=7 Hz), 6.4 (2H, d, J=8 Hz), 6.6 (2H, d, J=8 Hz), 7.4 (2H, t, J=8 Hz), 13.2 ppm (2H, s); MS *m/z* 370 (M^+), 259, 218. Found: C, 67.79, H, 6.04%. Calcd for $C_{21}H_{22}O_6$: C, 68.09, H, 5.99%. From the fraction soluble in a 10% sodium carbonate solution, ca. 20% of 2′,6′-dihydroxyacetophenone was recovered.

Similarly, cyclization of 2′,6′-dihydroxyacetophenone (20.0 mmol) with sodium hydride (23.3 mmol) and 1,4-dibromo-2-methyl-2-butene (21.6 mmol) gave **2** (1.85%), **4** (0.84%), and 1,4-bis(2-acetyl-3-hydroxyphenoxy)-2-methyl-2-butene (1.00%) and 40% of the starting material was recovered.

Cyclization of 2′,5′-Dihydroxyacetophenone with 1,4-Dibromo-2-methyl-2-butene. A similar treatment of 2′,5′-dihydroxyacetophenone (2.70 g, 17.8 mmol) with 1,4-dibromo-2-methyl-2-butene (4.30 g, 18.9 mmol) and sodium hydride (52% mineral oil dispersion, 0.84 g, 18.5 mmol) in dry toluene (90 mL) gave an oily product. This was purified on a silica-gel column and the fraction (total 282 mg) eluted by benzene showed two peaks (ratio **3**:**5**=2.2:1) in GLC. Some pure samples were obtained after re-chromatography and recrystallization. These two compounds showed the following data. **3**: mp 75—76 °C (from hexane); IR 1640 cm^{-1}; ^{1}H NMR cited in table 1; UV 233 (log ε 4.21), 261sh (3.90), 368 nm (3.65); MS *m/z* 218 (M^+), 203, 185, 177, 175. Found: C, 71.40, H, 6.67%. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47%. **5**: mp 96—98 °C (from hexane); IR 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.6 (3H, s), 2.6 (3H, s), 3.4 (1H, d, J=18 Hz), 3.5 (1H, d, J=18 Hz), 5.2 (1H, dd, J=1 and 11 Hz), 5.4 (1H, dd, J=1 and 17 Hz), 6.1 (1H, dd, J=11 and 17 Hz), 6.8 (1H, d, J=9 Hz), 7.0 (1H, d, J=9 Hz), 12.2 ppm (1H, s); UV 232 (log ε 4.31), 261sh (4.08), 366 nm (3.80); MS *m/z* 218 (M^+), 205, 175. Found: C, 71.78, H, 6.59%. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47%. From the fraction soluble in 10% sodium carbonate solution, ca. 50% of 2′,5′-dihydroxyacetophenone was recovered.

Similarly, in a cyclization of 2′,5′-dihydroxyacetophenone (7.83 mmol) with sodium hydride (17.4 mmol) and 1,4-dibromo-2-methyl-2-butene (7.89 mmol), a mixture (105 mg) of **3** and **5** (ratio **3**:**5**=2.4:1 in GLC) was obtained.

We wish to thank Professor Dr. Ferdinand Bohlmann for providing a copy of the ^{1}H NMR spectrum of the natural compound.

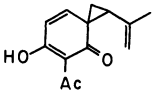
References

1) F. Bohlmann, J. Jakupovic, A. Schuster, R.M. King, and H. Robinson, *Phytochemistry*, **21**, 161 (1982).

2) S. Yamaguchi, K. Sugiura, R. Fukuoka, K. Okazaki, M. Takeuchi, and Y. Kawase, *Bull. Chem. Soc. Jpn.*, **57**, 3067 (1984).

3) F. Bigi, G. Casiraghi, G. Casnati, and G. Sartori, *Tetrahedron*, **39**, 169 (1983).

4) The oxepin derivative **4** may be formed via a cyclopropane intermediate **6**, which would be derived by a double C-alkylation. Mechanistic studies on the formation of **4** is now in progress.



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5) a) F.M. Dean and D. A. H. Taylor, *J. Chem. Soc. (C)*, **1966**, 114; b) P. H. McCabe, F. McCrindle, and R. D. H. Murray, *J. Chem. Soc. (C)*, **1967**, 145; c) Y. Asakawa, M. Toyota, and T. Takemoto, *Phytochemistry*, **17**, 2005 (1978).

6) The ^{1}H NMR spectrum of an impure sample showed that the compound **A** would be 7-acetyl-2-methyl-2-vinyl-2,3-dihydrobenzofuran-6-ol.