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Synthetic Studies of Sesamol Derivatives. XI.[*1] Synthesis of 5,6-Methylenedioxy-2-isopropenylbenzo[*b*]furan[*2]

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5,6-Methylenedioxy-2-isopropenylbenzo[*b*]furan, an analogue of the naturally-occurring 5,6-dimethoxy compound, has been synthesized by the dehydration of the corresponding 2-(1′-hydroxy)isopropyl derivative, which was obtained from 2-hydroxy-4,5-methylenedioxybenzaldehyde. By the catalytic hydrogenation of the benzofuran, its 2-isopropyl derivative and its 2-isopropyl-2,3-dihydrofurano-compound were prepared. The NMR spectra of these compounds have been compared.

Recently, a new naturally-occurring benzofuran derivative, 5,6-dimethoxy-2-isopropenylbenzo[*b*]furan (I), has been isolated from *Ligularia stenocephala* Matsum. *et* Koidz. by Takahashi *et al.*[1] 5,6-Methylenedioxy-2-isopropenylbenzo[*b*]furan(II), an analogue of I containing a methylenedioxy group instead of two methoxyl groups, has a substitution pattern found in several naturally-occurring flavonoids, isoflavonoids and coumestans; it could, therefore, be expected to occur in nature. It was considered useful to synthesize II and record its properties in order to help in the identification of the compound when it is discovered. In continuation of a series of synthetic studies of sesamol deriv-

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[*1] Part X: K. Fukui and M. Nakayama, This Bulletin, **41**, 2733 (1968).

[*2] Presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968.

1) T. Murae, Y. Tanahashi and T. Takahashi, *Tetrahedron*, **24**, 2177 (1968).

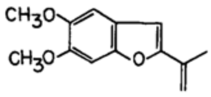
atives, the present paper will describe the syntheses of II and related compounds, and will present the spectral data of these compounds.

The reaction of methylmagnesium iodide with 5,6-methylenedioxy-2-acetylbenzo[*b*]furan (III), which was obtained by treating 2-hydroxy-4,5-methylenedioxybenzaldehyde (IV)[2] with monobromoacetone, afforded a benzofuran derivative V, $C_{12}H_{12}O_4$, mp 65—66°C. The same compound, V, was furnished by the reaction of this Grignard reagent with 5,6-methylenedioxy-2-carbethoxybenzo[*b*]furan (VI).[3] The infrared spectrum of V exhibited an absorption due to the hydroxyl group at 3320 cm^{-1}. In its NMR spectrum (Table 1),[*3] a singlet signal at δ 2.10 (1H), which easily disappeared upon deuterium exchange, and a sharp singlet at δ 1.63 (6H) provided evidence for the presence of $-C(OH)(CH_3)_2$ grouping. Moreover, V has the NMR signals at δ 5.97 (singlet, 2H, O–CH_2–O), 6.46 (doublet, 1H, J=0.75 Hz, β-hydrogen atom of benzofuran ring),[4] 6.90 (singlet, 1H, aromatic proton), and 6.97 (doublet, 1H, J=0.75 Hz, aromatic proton). These NMR spectral data suggest the presence of one β-proton on the benzofuran ring and that the two isolated aromatic protons are in a 1,4-relationship. Therefore, the structure of V was established as 5,6-methylenedioxy-2-(1′-hydroxy) isopropylbenzo[*b*]furan.

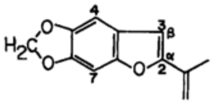
The dehydration of V by heating alone afforded an isopropenyl derivative II, $C_{12}H_{10}O_3$, mp 98—99°C, in a 41% yield. The NMR spectrum of II (Table 1 and Fig. 1) showed a methyl signal, δ 2.09 (3H, doublet, J=Hz), and signals due to two vinyl protons at δ 5.12 and 5.70 (each 1H, finely-split signal).

The catalytic hydrogenation of II over 5% Pd-C in ethyl acetate at room temperature gave the corresponding isopropylbenzofuran VII, $C_{12}H_{12}O_3$, mp 56—57°C; its NMR spectrum exhibited signals at δ 1.29 (6H, doublet, J=7 Hz), 3.02 (1H, multiplet, $(CH_3)_2$=CH–), 6.89 (1H, singlet), and 6.97 (1H, broad singlet). Elvidge and Foster[4] have reported that, in the NMR spectra of benzofurans, the 3-proton couples with the 7-proton with J=0.9 Hz. The singlet at δ 6.89 and the broad singlet at δ 6.97 mentioned above can, therefore, be attributed to the 4- and 7-protons respectively. This assumption is in accord with the spectral data (Table 1) of 4,5-methylenedioxybenzo[*b*]furan (VIII)[3] and its 3-methyl- (IX) and 2,3-dimethyl-derivative (X) prepared from sesamol.[5]

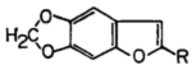
Next, VII was further reduced over 5% Pd-C in ethanol at an elevated temperature to give 2,3-dihydrobenzofuran, XI. The NMR spectrum of XI (Table 1 and Fig. 3) showed a two-proton



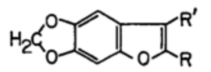
I



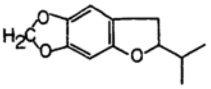
II



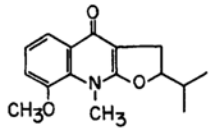
III R=$COCH_3$
V R=$C(OH)(CH_3)_2$
VI R=$CO_2C_2H_5$
VII R=$CH(CH_3)_2$



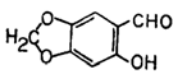
VIII R=R′=H
IX R=H, R′=CH_3
X R=R′=CH_3



XI



XII



IV

TABLE 1. THE NMR SPECTRAL DATA OF BENZO[*b*]-FURANS[*3,4]

Benzo[*b*]-furan	Proton			
	C-2	C-4	C-3	C-7
II	—	6.93_s	6.57_{bs}	6.99_d (J=1)
III	—	7.02_m	7.42_d J=0.75)	7.02_m
V	—	6.90_s	6.46_d (J=0.75)	6.97_d (J=0.75)
VI	—	6.99_s	7.45_d (J=1)	7.07_m
VII	—	6.89_s	6.25_m	6.97_{bs}
XI	4.46_m	6.62_s	$2.56—3.28_m$	6.35_s
VIII	7.58_d (J=2)	6.99_s	6.68_{dd} (J=2, J=1)	7.05_d (J=1)
IX	7.35_q (J=1.5)	6.90_s or 6.97	—	6.97_s or 6.90_s
X	—	6.82_s or 6.92_s	—	6.92_s or 6.82_s

[*4] s=singlet, bs=broad singlet, d=doublet, q=quartet, m=multiplet, and dd=double doublet and J=Hz value.

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[2] K. Fukui and M. Nakayama, This Bulletin, **35**, 1321 (1962).

[3] K. Fukui, M. Nakayama and K. Okazaki, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **87**, 1096 (1966).

[*3] The NMR spectra were measured with a Hitachi R-20 spectrometer, using tetramethylsilane as the internal standard (δ-value in $CDCl_3$).

[4] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, **1964**, 981.

[5] K. Fukui and M. Nakayama, *J. Sci. Hiroshima Univ., Ser. A-II*, **26**, 131 (1963).

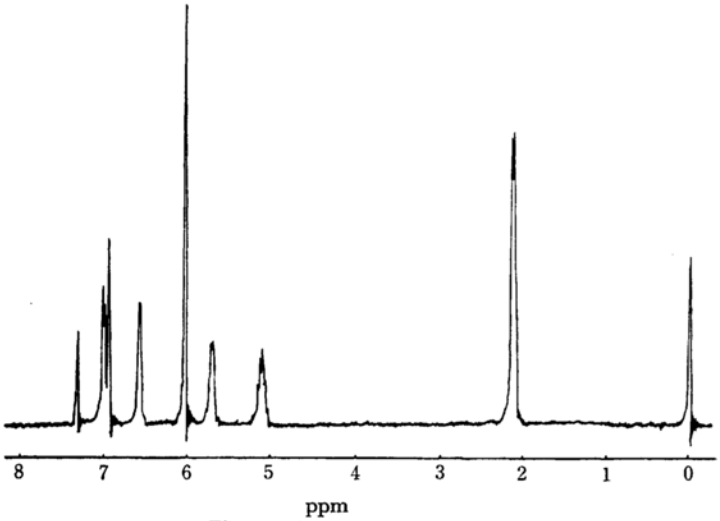

Fig. 1. NMR spectrum of II.

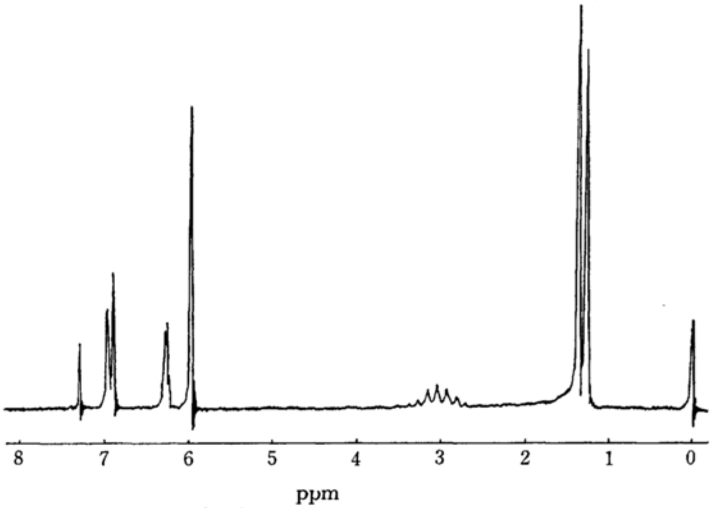

Fig. 2. NMR spectrum of VII.

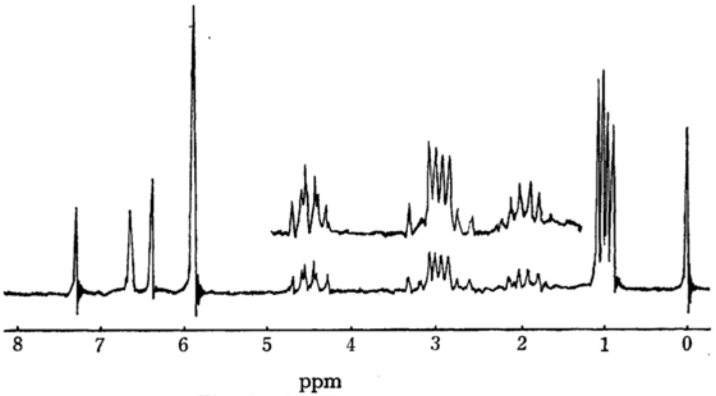

Fig. 3. NMR spectrum of XI.

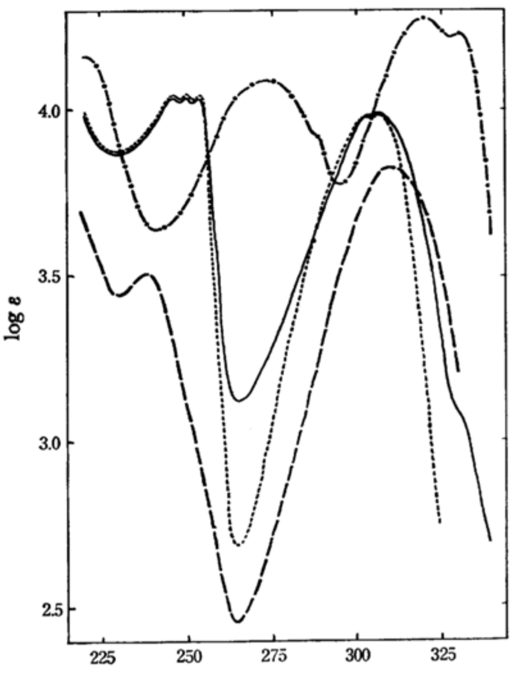

Fig. 4. Ultraviolet spectra of II (–·–·–), V (——), VII (------) and XI (— — —) in ethanol.

multiplet centered at δ *ca.* 2.9 and a one-proton multiplet centered at δ 4.46 attributable to the β- and α-protons of dihydrofuran-ring respectively. An interesting feature of the spectrum was provided by the signals (δ 0.93 and 0.99, each 3H, doublet, J=6.5 Hz) due to the two methyl groups of the isopropyl side chain; *e. g.*, these signals are quite similar to those of the isopropyldihydrofuran system in lunacrine (XII),[6] and these two methyl groups are magnetically nonequivalent.

The ultraviolet spectra of these compounds (II, V, VII, and XI) are shown in Fig. 4. The shape of the UV spectrum of V is very similar to that of VII. The bathochromic effect (about 11 mμ) observed in the spectrum of II could be explained as resulting from the isopropenyl double bond conjugated to the furan ring at the α-position. On the other hand, the spectrum of XI is very similar to that of 6-substituted-3,4-methylenedioxyanisole derivatives.[7]

Experimental[*5]

5,6-Methylenedioxy-2-acetylbenzo[*b*]furan (III). A hot solution of IV (mp 125—126°C)[2] (3.3 g) in absolute ethanol (40 m*l*) was treated with a solution of potassium hydroxide (1.2 g) in absolute ethanol (20 m*l*). Then, monobromoacetone (3.0 g) was stirred, drop by drop, into the hot solution over a 20-min period and the reaction mixture was refluxed for 1 hr on a steam bath. Again, potassium hydroxide (0.6 g) and monobromoacetone (1.5 g) were added to the mixture and the reaction was continued for 1 hr. The product was treated again with potassium hydroxide (0.3 g) and monobromoacetone (0.75 g). After the addition of water (20 m*l*), the organic solvent was evaporated. The resulting residue was repeatedly extracted with benzene. The combined benzene solutions were washed with a diluted sodium hydroxide solution, dried over anhydrous sodium sulfate, and evaporated. The residue was crystallized from ethanol to give colorless needles of III, mp 156.5—157°C; yield, 3.2 g. IR: 1672 (C=O); 1626, 1545, 1495 (aromatic); 1036, 945 cm^{-1} (O–CH$_2$–O). UV: λ_{max} mμ (log ε); 267 (3.76), 291.5 (4.00), 340 (4.27). NMR:[*3,4] δ 6.05$_s$ (O–C$\underline{H}_2$–O), 2.55$_s$ (C$\underline{H}_3$CO) and Table 1.

Found: C, 64.95; H, 4.14%. Calcd for $C_{11}H_8O_4$: C, 64.70; H, 3.95%.

5,6-Methylenedioxy-2-(1′-hydroxy)isopropylbenzo[*b*]furan (V). *a*) *From III.* A solution of III (510 mg) in a mixture of anhydrous ether (10 m*l*) and anhydrous benzene (35 m*l*) was slowly stirred into a methylmagnesium iodide solution (from methyl iodide (1.56 g) and magnesium (270 mg) in anhydrous ether (15 m*l*)) for 0.5 hr in an ice-bath. After stirring for 1.5 hr, the reaction mixture was decomposed by the cautious addition of 1 N sulfuric acid (20 m*l*). The aqueous layer was reextracted with benzene, and the combined benzene solution were washed with a 5% sodium hydrogen carbonate solution and a saturated sodium thiosulfate solution, and dried over anhydrous sodium sulfate. After the solvent had been evaporated *in vacuo*, the residue was purified by column chromatography over alumina with benzene. The elute was evaporated to yield yellow crystals. This was sublimated at 50°C *in vacuo* to give colorless crystals of V, mp 65—66°C; yield, 160 mg. IR: 3320 (OH); 1630, 1591, 1555, 1505 (aromatic); 1040, 938 cm^{-1} (O–CH$_2$–O). UV: λ_{max} mμ (log ε); 246.5 (4.03), 250.5 (4.03), 254.5 (4.03), 306$_{sh}$[*6] (3.98), 309 (3.98), 331$_{sh}$ (3.10). NMR:[*3,4] δ 5.97$_s$ (O–C$\underline{H}_2$–O); 2.10$_s$ (O$\underline{H}$); 1.63$_s$ (6H, C$\underline{H}_3$) and Table 1.

Found: C, 65.57; H, 5.29%. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49%.

b) *From VI.* A mixture of VI (mp 84—85°C)[3] (1.1 g) in anhydrous ether (10 m*l*) and anhydrous benzene (20 m*l*), and a methylmagenesium iodide solution (from methyl iodide (2.20 g) and magnesium (0.35 g) in anhydrous ether (10 m*l*)) was refluxed on a steam bath with stirring for 1.5 hr. The reaction mixture was then treated as above to give V, mp 65—66°C; yield, 0.55 g.

5,6-Methylenedioxy-2-isopropenylbenzo[*b*]furan (II). The hydroxy-compound V (160 mg) was heated at 150°C for 5 min in a stream of nitrogen. The viscous, orange yellow product was sublimated in a stream of nitrogen *in vacuo* at 90°C/1 mmHg to give colorless needles of II, mp 98—99°C; yield, 60 mg.

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6) S. Goodwin, J. N. Shoolery and L. F. Johnson, *J. Am. Chem. Soc.*, **81**, 3065 (1959).

7) K. Fukui and M. Nakayama, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **84**, 606 (1963).

[*5] All the melting points are uncorrected; the infrared spectra were measured in Nujol, while the ultraviolet spectra were measured in ethanol.

[*6] sh=shoulder.

IR: 1620, 1555, 1502 (aromatic); 1038, 940 (O–C$\underline{H}_2$–O); 877 cm^{-1} (H_2C=C<). UV: λ_{max} mμ (log ε); 221 (4.16), 276 (4.07), 320 (4.26), 332 (4.22). NMR:[*3,4] δ 6.00_s (O–C$\underline{H}_2$–O); 5.70_m, 5.12_m (each IH, >C=C$\underline{H}_2$); 2.09_d (J=1)(C$\underline{H}_3$) and Table 1.

Found: C, 71.14; H, 5.12%. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99%.

5,6-Methylenedioxy-2-isopropylbenzo[*b*]furan (VII). A solution of II (65 mg) in ethyl acetate (50 m*l*) was hydrogenated over 5% Pd-C (50 mg) at room temperature for 10 min; 1 molar equivalent of hydrogen was absorbed. After the catalyst had been filtered, the filtrate was evaporated under a weak vacuum. The residual oil was soon crystallized on cooling. This was sublimated *in vacuo* at 55°C/0.5 mmHg to give colorless prisms of VII, mp 56—57°C; yield, 57 mg. IR: 1625, 1588, 1555, 1500 (aromatic); 1036, 943 cm^{-1} (O–C$\underline{H}_2$–O). UV: λ_{max} mμ (log ε); 247 (4.04), 251 (4.03), 255 (4.04), 305 (3.97), 309 (3.97). NMR:[*3,4] δ 5.96_s (O–C$\underline{H}_2$–O); 3.02_m (J=7)(⋗C$\underline{H}$); 1.29_d (J=7)(6H, C$\underline{H}_3$) and Table 1.

Found: C, 70.39; H, 5.88%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%.

5,6-Methylenedioxy-2-isopropyl-2,3-dihydrobenzo[*b*]furan (XI). A solution of VII (40 mg) in ethanol was hydrogenated over 5% Pd-C at 70°C at atmospheric pressure for a few hours. After the same procedure as has been described above, the residue was crystallized from dilute ethanol to give colorless plates of XI; mp 92—93°C; yield, 37 mg. IR: 1616, 1498 (aromatic); 1047, 934 cm^{-1} (O–C$\underline{H}_2$–O). UV: λ_{max} mμ (log ε); 240 (3.51), 313 (3.82). NMR:[*3,4] δ 5.85_s (O–C$\underline{H}_2$–O); 1.93_m (J=6.5) (⋗C$\underline{H}$); 0.99_d, 0.93_d (J=6.5) (each 3H, C$\underline{H}_3$) and Table 1.

Found: C, 70.09; H, 6.67%. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84%.

5,6-Methylenedioxy-3-methylbenzo[*b*]furan (IX). *a*) *2-Acetyl-4,5-methylenedioxyphenoxyacetic Acid.* A mixture of 2-hydroxy-4,5-methylenedioxyacetophenone (mp 112—113°C)[8)] (0.9 g), ethyl bromoacetate (0.9 g), and anhydrous potassium carbonate (4.0 g) in anhydrous acetone (100 m*l*) was refluxed for 7 hr in a steam bath, and then the inorganic precipitates were filtered off. After the filtrate had been evaporated, the residue was added to a 2N sodium hydroxide solution (60 m*l*). The mixture was heated in a steam bath for 0.5 hr and then acidified with 2N hydrochloric acid. The resulting precipitate was collected and recrystallized from ethyl acetate to give 2-acetyl-4,5-methylenedioxyphenoxyacetic acid as colorless needles, mp 205°C; yield, 0.6 g. IR: 1734, 1711, 1654 (C=O); 1620, 1500 (aromatic); 1043, 932 cm^{-1} (O–CH$_2$–O).

Found: C, 55.69; H, 4.23%. Calcd for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23%.

b) *5,6-Methylenedioxy-3-methylbenzo[b]furan* (*IX*). A mixture of the above phenoxyacetic acid (0.6 g), anhydrous sodium acetate (10 g), and acetic anhydride (100 m*l*) was vigorously refluxed for 3 hr. The cooled mixture was then poured into water. The resulting precipitate was collected and recrystallized from ethanol to give IX as colorless needles, mp 56—56.5°C; yield, 0.4 g. IR: 1621, 1585, 1504 (aromatic); 1038, 939 cm^{-1} (O–CH$_2$–O). UV: λ_{max} mμ (log ε); 248.5 (3.92), 256 (3.83), 303 (3.90), 308 (3.90). NMR:[*3,4] δ 5.98_s (O–C$\underline{H}_2$–O); 2.17_d (J=1.5)(C$\underline{H}_3$).

Found: C, 67.92; H, 4.51%. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58%.

5,6-Methylenedioxy-2,3-dimethylbenzo[*b*]furan (X). To a solution of sesamol[5)] (5.0 g) and 3-chlorobutanone-2 (3.9 g) in anhydrous methyl ethyl ketone (150 m*l*), anhydrous potassium carbonate (20 g) and potassium iodide (12 g) were added. The resulting mixture was refluxed for 17 hr in a steam bath, and then the inorganic precipitates were filtered off. After the filtrate had been evaporated, the residue was distilled *in vacuo* to give methyl α-(3,4-methylenedioxyphenoxy) ethyl ketone as a colorless oil, bp 163—165°C/23 mmHg; yiled, 3.0 g.

A mixture of the above ketone (3.0 g) and polyphosphoric acid (n=2.5; 18 g) was kept at room temperature for 2 days. The reaction mixture was then poured into a 2N sodium hydroxide solution. The resulting precipitate was collected and recrystallized from ethanol to give X as colorless needles, mp 82—83°C; yield, 1.5 g. IR: 1643, 1619, 1496 (aromatic); 1034, 938 cm^{-1} (O–CH$_2$–O). UV: λ_{max} mμ (log ε); 251 (3.96), 307 (3.95), 311 (3.95). NMR:[*3,4] δ 5.96_s ((O–C$\underline{H}_2$–O); 2.32_s, 2.07_s (each 3H, C$\underline{H}_3$).

Found: C, 69.47; H, 5.14%. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30%.

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8) K. Fukui and M. Nakayama, This Bulletin, **37**, 300 (1964).