BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 2918—2919 (1973)

Synthesis of Dihydrofarfugin B

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(Received April 2, 1973)

Farfugin A (I) and farfugin B (II) have been isolated from the benzene extract of *Farfugium japonicum* Kitamura (=*Ligularia tussilaginea* Makino). Spectral data of the latter and its derivatives led to two alternative structures, II and III for farfugin B. The structure of farfugin B was finally deduced to be 3,5-dimethyl-6-(*trans*-*n*-3-pentenyl)benzofuran (II) on the basis of NOE (Nuclear Overhauser Effect) experiments.[1,2]

We report here the synthesis of dihydrofarfugin B (IV); this confirms the structure of II for farfugin B.

Grignard reagent prepared from 1-methyl-2-bromo-4-methoxybenzene (V)[3] was treated with *n*-pentanal to give an alcohol (VI). Dehydration of VI with iodine[4] gave the dehydrated product (VII), which was subjected to hydrogenation over Pd–C to afford VIII. Demethylation of VIII with hydrobromic acid in acetic acid gave a phenol (IX).

Finally the furan moiety was introduced as follows. Phenoxyacetone (X), prepared from the reaction of the phenol (IX) with chloroacetone, was cyclized with polyphosphoric acid on heating. This cyclization occurred toward two directions to give two isomeric benzofuran derivatives, (IV) and (XI), in the ratio of 5: 2. The PMR spectrum of the minor component showed a signal of AB type quartet (δ_A=6.91 and δ_B=7.03 ppm; J=9 Hz) due to the aromatic *ortho*-

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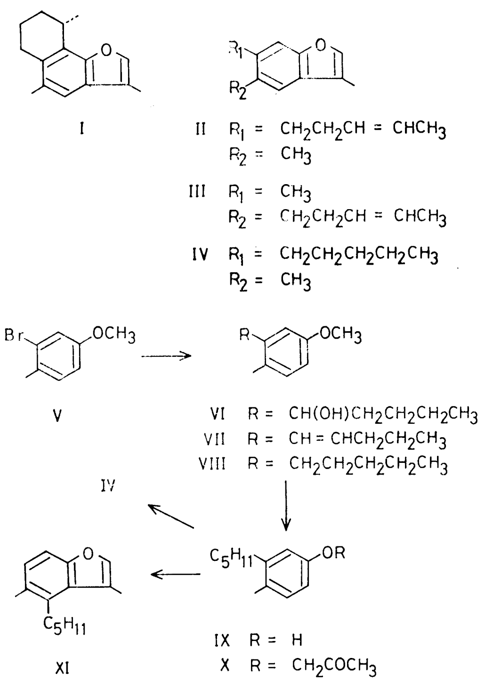
[1] H. Nagano, Y. Moriyama, Y. Tanahashi, T. Takahashi, M. Fukuyama, and K. Sato, *Chemistry Lett.*, **1972**, 13.

[2] M. Tada, Y. Moriyama, Y. Tanahashi, and T. Takahashi, *Tetrahedron Lett.*, **1972**, 5251; M. Tada, Y. Tanahashi, Y. Moriyama, and T. Takahashi, *ibid.*, **1972**, 5255.

[3] E. Müller, A. Rieker, and K. Scheffler, *Ann.*, **645**, 92, (1961).

[4] B. A. Nagasampagi, Sukh Dev, C. Rai, and K. L. Murthy, *Tetrahedron*, **22**, 1971 (1966).



protons. This led to the structure of 3,5-dimethyl-4-*n*-pentylbenzofuran (XI) for the minor component. The major one was consequently assigned to be 3,5-dimethyl-6-*n*-pentylbenzofuran (IV), which was found to be identical with dihydrofarfugin B in all respects (IR, PMR, UV, and mass spectra). The presence of *trans*-*n*-3-pentenyl side chain was already shown for farfugin B.$^{1)}$ Thus, the structure of farfugin B was confirmed to be 3,5-dimethyl-6-(*trans*-*n*-3-pentenyl) benzofuran (II).

Experimental

IR spectra were taken in neat film, and PMR spectra were measured in $CDCl_3$ containing TMS as internal standard.

*1-(1-Hydroxy-*n*-pentyl)-2-methyl-5-methoxybenzene (VI).* To the Grignard reagent prepared from 1-methyl-2-bromo-4-methoxybenzene (V)$^{3)}$ (12.1 g, 58 mmol) in dry tetrahydrofuran (50 ml) and magnesium ribbon (1.75 g, 72 mmol), a solution of *n*-pentanal (6.02 g, 70 mmol) in dry tetrahydrofuran (20 ml) was added dropwise and stirred for 1 hr at room temperature. The reaction material was poured on a mixture of crashed ice (100 g) and concentrated hydrochloric acid (10 ml). This was extracted with ether three times (each 100 ml). After usual work-up, the extract gave a residue (14.0 g) containing VI, a part of which was purified by chromatography on silica gel with benzene as eluent to give pure VI, an oil, IR: ν_{max} 3380 cm^{-1} (OH); PMR: δ 0.90 (m, terminal $C\underline{H}_3$ on a side chain), 2.24 (s, aromatic $C\underline{H}_3$), 3.79 (s, $OC\underline{H}_3$), 4.88 (t, J=6 Hz, $-\overset{|}{C}\underline{H}-OH$), and 6.50—7.10 (aromatic protons); MS: *m/e* 208 (M^+; $C_{13}H_{20}O_2$). Found: C, 74.91; H, 9.72%. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%.

*1-(*n*-1-Pentenyl)-2-methyl-5-methoxybenzene (VII).* The above residue (3.51 g) was heated with iodine (170 mg)$^{4)}$ at 100 °C for 3 hr. The reaction mixture was chromatographed on silica gel (150 g) with benzene as eluent to afford VII (2.23 g; yield 78% from V), an oil, PMR: δ 0.95 (m, terminal $C\underline{H}_3$), 2.18 (m, 2H, allylic protons), 2.24 (s, aromatic $C\underline{H}_3$), 3.78 (s, $OC\underline{H}_3$), and 6.10—7.30 (aromatic and olefinic protons); MS: *m/e* 190 (M^+; $C_{13}H_{18}O$). Found: C, 81.88; H, 9.68%. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54%.

*1-*n*-Pentyl-2-methyl-5-methoxybenzene (VIII).* Hydrogenation of VII (1.16 g, 6.1 mmol) was effected in ethanol over 10% palladium-charcoal. After usual treatment, VIII (926 mg; yield 79%), an oil, was obtained. Characterization of VIII is as follows; PMR: δ 0.89 (m, terminal $C\underline{H}_3$), 2.21 (s, aromatic $C\underline{H}_3$), 2.54 (m, 2H, benzyl protons), 3.74 (s, $OC\underline{H}_3$), and 6.50—7.20 (aromatic protons); MS: *m/e* 192 (M^+; $C_{13}H_{20}O$). Found: C, 81.28; H, 10.68%. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48%.

*1-*n*-Pentyl-2-methyl-5-hydroxybenzene (IX).* To a solution of VIII (0.79 g, 4.1 mmol) in acetic acid (5 ml), 48% hydrobromic acid (5 ml) was added and the mixture was heated under reflux for 20 hr. Acetic acid was removed under reduced pressure and ether (100 ml) was added to the residue. The ether solution was washed with saturated aqueous solution of sodium bicarbonate and then treated as usual. The residue was chromatographed on silica gel (50 g) with benzene as eluent to give IX (285 mg; yield 39%), an oil, IR: ν_{max} 3380 cm^{-1} (OH); PMR: δ 0.88 (m, terminal $C\underline{H}_3$), 2.19 (s, aromatic $C\underline{H}_3$), 2.49 (m, 2H, benzyl protons), 5.57 (s, $O\underline{H}$), and 6.45—7.10 (aromatic protons); MS: *m/e* 178 (M^+; $C_{12}H_{18}O$). Found: C, 80.87; H, 10.48%. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18%.

*1-*n*-Pentyl-2-methyl-5-acetonyloxybenzene (X).* A solution of IX (266 mg, 1.5 mmol) in dry acetone (10 ml) was heated under reflux with chloroacetone (299 mg) and potassium iodide (130 mg) for 20 hr. The solvent was distilled off and ether (100 ml) was added to the residue, and the ether solution was treated as usual. The residue was chromatographed on silica gel (30 g) with benzene as eluent to afford X (252 mg; yield 72%), an oil, IR: ν_{max} 1720 cm^{-1} (CO); PMR: δ 0.90 (m, terminal $C\underline{H}_3$), 2.16 (s, 6H, aromatic $C\underline{H}_3$ and $-COC\underline{H}_3$), 2.51 (m, 2H, benzyl protons), 4.35 (s, $-OC\underline{H}_2CO-$) and 6.40—7.02 (aromatic protons); MS: *m/e* 234 (M^+; $C_{15}H_{22}O_2$). Found: C, 76.64; H, 9.48%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

*3,5-Dimethyl-6-*n*-pentylbenzofuran (IV) and 3,5-Dimethyl-4-*n*-pentylbenzofuran (XI).* Acetonyloxy derivative (X) (200 mg, 0.86 mmol) was heated with polyphosphoric acid (4 g) at 100 °C for 10 min under a nitrogen atmosphere. After cooling, the reaction material was poured on a mixture of crashed ice (50 g) and concentrated hydrochloric acid (5 g) to decompose the excess polyphosphoric acid. This was extracted with ether and the ethereal solution was washed with saturated aqueous solution of sodium bicarbonate (100 ml) and then treated as usual. The residue obtained was chromatographed on silica gel to give a mixture (45.4 mg; yield 25%) of IV and XI. The mixture was further chromatographed using 20% $AgNO_3$-impregnated silica gel with petroleum ether as eluent and IV (17.7 mg) and XI (7.5 mg) were obtained. Spectral data of IV, an oil, are as follows; IR: ν_{max} 1625, 1580, 800, 780 cm^{-1}; PMR: δ 0.90 (m, terminal $C\underline{H}_3$), 2.20 (d, J=2 Hz, $C\underline{H}_3$ on a furan ring), 2.38 (s, aromatic $C\underline{H}_3$), 2.66 (m, 2H, benzyl protons), and 7.05—7.20 (protons on a furan and a benzene ring); UV: λ_{max}^{EtOH} 251.5 nm (ε 11300); MS: *m/e* 216 (M^+; $C_{15}H_{20}O$). The compound IV was found to be identical with dihydrofarfugin B (IR, PMR, UV, and mass spectra).

Characterization of XI, an oil, is as follows; IR: ν_{max} 1580, 780 cm^{-1}; PMR: δ 0.93 (m, terminal $C\underline{H}_3$), 2.36 (two methyl groups on a furan and a benzene ring), 2.87 (m, 2H, benzyl protons), 6.97 (an AB quartet, δ_A=6.91, δ_B=7.03, J=9 Hz), and 7.16 (d, J=2 Hz, a proton on a furan ring); UV: λ_{max}^{EtOH} 254.3 nm (ε 12400); MS: *m/e* 216 (M^+; $C_{15}H_{20}O$). Found: C, 83.06; H, 9.55%. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32%.