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FARFUGIN A AND B, NEW SESQUITERPENES FROM FARFUGIUM JAPONICUM

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Two new sesquiterpenes, farfugin A and B, isolated from Farfugium japonicum, have been shown to be a tetrahydronaphthofuran derivative (I) and a benzofuran derivative (II), respectively.

Farfugium japonicum (L.) Kitam. (= Ligularia tussilaginea Makino ; Tsuwabuki in Japanese) spreads over on the south-western part of Japan, and its constituents have been studied by several groups of workers.1) In connection with our chemical investigation on the genus Ligularia, we have examined the benzene extract of the rhizome of this plant, and isolated two new sesquiterpenes, farfugin A and B, by means of vacuum distillation followed by column chromatography over silica gel. We describe here the evidence leading to the structures I and II for farfugin A and B, respectively. These structures are related to the rearranged frameworks derived from furanoeremophilane derivatives.

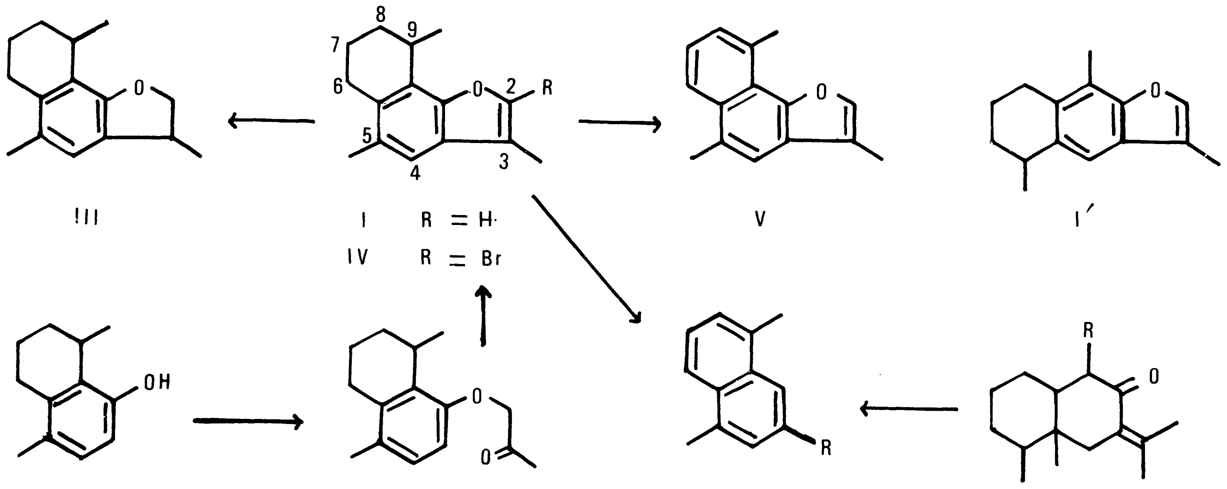
Farfugin A (I) has a molecular formula of $C_{15}H_{18}O$, M^+ 214, m.p. 80.5-82.5°, $[\alpha]_D$ + 39°. The IR spectrum of I shows neither carbonyl nor hydroxyl absorption. The UV (λ_{max} 252.5 nm, ε 14500 ; 281 nm, ε 2800 ; 291 nm, ε 3200) and PMR spectra [in $CDCl_3$; an α-proton (δ 7.20 ppm, m) and a β-methyl (δ 2.16 ppm, d, J = 1.2 Hz) on a furan ring] suggest the presence of a β-methyl substituted benzofuran moiety;2) this was confirmed by the formation of dihydrofarfugin A (III ; $C_{15}H_{20}O$, M^+ 216, m.p. 51-52°) on hydrogenation (Pd-C, MeOH), and of bromofarfugin A (IV ; $C_{15}H_{17}OBr$, M^+ 294 and 292, m.p. 99.5-100°) on bromination. Furthermore, the PMR spectrum reveals the nature of all protons in I : an aromatic proton (δ 7.05 ppm, s), an aromatic methyl (δ 2.27 ppm, s), a secondary methyl (δ 1.37 ppm, d, J = 7.5 Hz) spin-coupled with a benzylic proton (δ 3.35 ppm, m), two other benzylic protons (δ 2.63 ppm, m) and four aliphatic protons (δ 1.5-2.0 ppm).

Dehydrogenation of I over Pd-C afforded a naphthofuran derivative (V)3), $C_{15}H_{14}O$, M^+ 210, m.p. 64.5-65.5°, λ_{max} 248.5, 253, 282.5, 291, 302, 324 and 339 nm (ε 49300, 48400, 5330sh, 5770, 4280sh, 1750 and 1510, respectively) and a mixture of two naphthalene derivatives. Although the separation of the latter compounds failed, the PMR, IR, UV and mass spectra of the authentic 1,5-dimethyl-3-isopropylnaphthalene (VI)4) prepared from fukinone (VII)5) via VIII gave a sufficient evidence that the mixture consisted of VI and 1,5-dimethyl-3-ethylnaphthalene (IX).

TABLE Nuclear Overhauser Effects$^{a)}$
(increases in integrated signal intensities, %)

Observed proton	Saturated protons	NOE (IV)	Observed protons	Saturated protons	NOE (XII)
4-H (7.00s)	3-Me (2.12s)	7	4-H (6.88s)	5-Me (2.23s)	14
4-H	5-Me (2.27s)	15	7-H (6.58s)	5-Me	nil
4-H	9-Me (1.38d, J=7)	nil	4-H	3-H (3.45m)	3
			7-H	3-H	nil
			1'-H (2.52m)	4-H (6.88s)	nil
			3-Me (1.29d, J=7)	7-H (6.58s)	nil
			1'-H	7-H	9
			4-H	1'-H (2.52m)	nil
			7-H	1'-H	19

a) The PMR spectra were taken with a Varian HA-100 spectrometer operating at 100 MHz in the frequency-swept and internal TMS-locked mode, for ca. 5% (w/v) degassed solutions in CDCl$_3$. Chemical shifts are expressed in δ ppm downfield from TMS and coupling constants in Hz. NOE experiments were performed with sweep rates of 0.4 Hz per sec for integrations and 0.2 Hz per sec for signals on the spectrometer with a Hewlett-Packard HP-200ABR audio-oscillator and an HP-5212A electronic counter. Accuracies for NOE values are about ± 2 %.



III

I $R = H$
IV $R = Br$

V

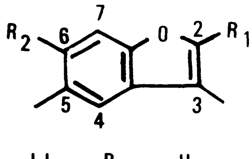
I'

X

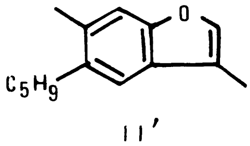
XI

VI $R = CH(CH_3)_2$
IX $R = CH_2CH_3$

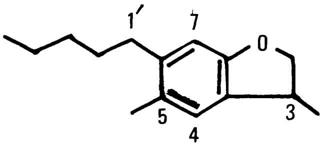
VII $R = H$
VIII $R = CH_3$



II $R_1 = H$, $R_2 = CH_2CH_2CH{=}CHCH_3$
XIII $R_1 = Br$, $R_2 = CH_2CH_2CH{=}CHCH_3$
XIV $R_1 = Br$, $R_2 = CH_2CH_2CHBrCHBrCH_3$
XV $R_1 = H$, $R_2 = CH_2CH_2CH_2CH_2CH_3$



II'



XII

From two alternative structures (I and I') for farfugin A, which are compatible with the above observations, I' could be eliminated because of the observed intramolecular nuclear Overhauser effects (NOE)$^{6)}$ between the aromatic proton (4-H) and the aromatic methyl (5-Me), and between the same aromatic proton (4-H) and the methyl (3-Me) on the furan ring for IV (Table).

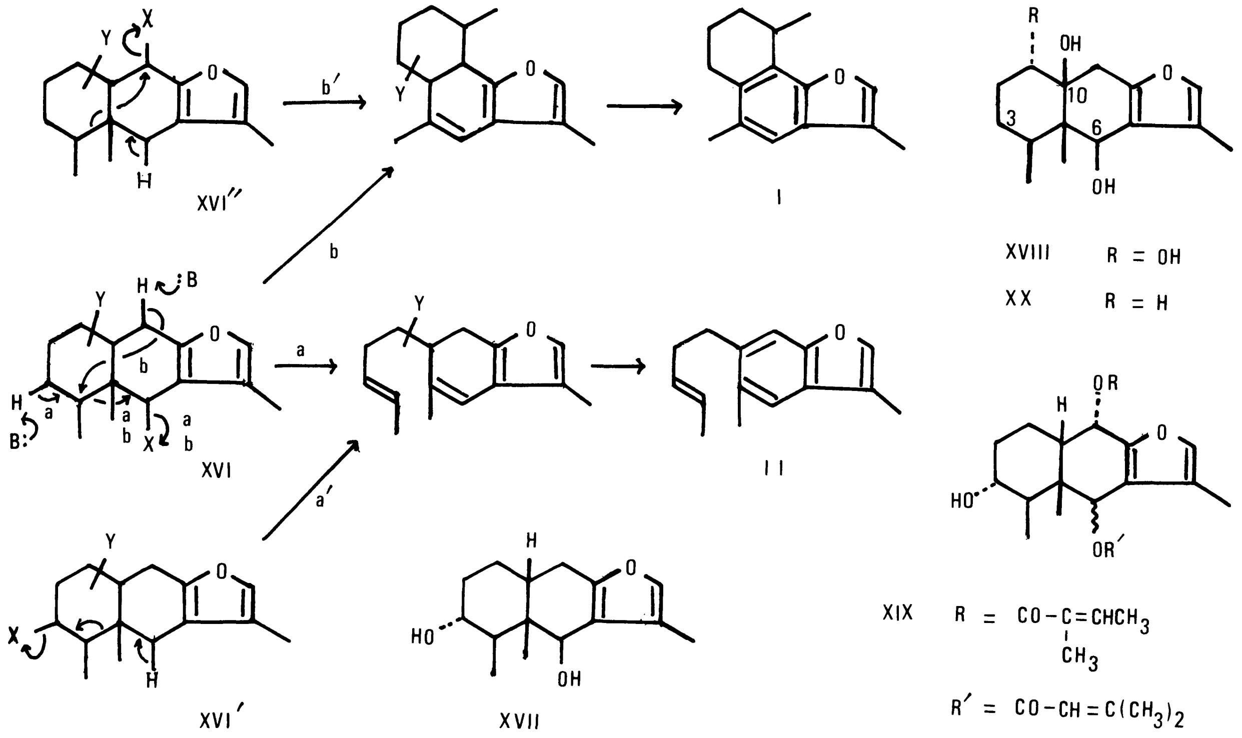
Finally, the following synthesis afforded a conclusive evidence ; on refluxing with chloroacetone, potassium iodide and potassium carbonate in dry acetone, 5,6,7,8-tetrahydro-4,8-dimethyl-1-naphthol (X)$^{7)}$ gave an oily keto-ether (XI), which was then heated with polyphosphoric acid (100°, 35 min, under N_2) to give (±)-I, m.p. 73-73.5°, identical with natural I in all respects [IR in nujol (I is soluble in nujol) ; PMR ; UV ; MS ; TLC and VPC] except $[\alpha]_D$ data.

Farfugin B (II), $C_{15}H_{18}O$, M^+ 214, a colourless oil, is isomeric with farfugin A (I). The UV (λ_{max} 251.5 nm, ε 10500 ; 281.5 nm, ε 3550; 291.5 nm, ε 3900) and PMR spectra [in $CDCl_3$; a β-methyl on a furan ring (δ 2.19 ppm, d, J = 1.2 Hz)] show the presence of a β-methyl substituted benzofuran moiety. The PMR spectrum also indicates the presence of an aromatic methyl (δ 2.37 ppm, s), three aromatic protons (δ 7.2, m ; including an α-proton of the furan ring), an olefinic methyl (δ 1.65 ppm, m) and two olefinic protons (δ 5.00 ppm, m, and 5.45 ppm, m).

In the PMR spectrum of tetrahydrofarfugin B (XII), $C_{15}H_{22}O$, M^+ 218, oil, obtained by hydrogenation (Pd-C, MeOH) of II, there appear a multiplet (as AM part of an AMX system ; δ 4.01 and δ 4.63 ppm ; $-O-\underline{CH_2}-CH-$) due to a methylene of dihydrofuran moiety, and two <u>singlets</u> (δ 6.59 and 6.90 ppm) due to two aromatic protons. Thus, farfugin B is a 3-methylbenzofuran derivative having a methyl and a C_5H_9 substituent on C-5 and C-6 (either II or II').

The C_5H_9 group was shown to be 3-<u>trans</u>-pentenyl from the following results. The olefinic methyl signal in the PMR spectrum of II is replaced by a doublet (δ 1.86 ppm, d, J = 7.5 Hz) due to a methyl on a bromine-carrying carbon in the spectrum of tribromofarfugin B (XIV), $C_{15}H_{17}OBr_3$, M^+ 456, 454, 452 and 450, m.p. 74-74.5° ; this tribromo-derivative (XIV) was formed together with bromofarfugin B (XIII), $C_{15}H_{17}OBr$, M^+ 294 and 292, m.p. 36-37°, on bromination of II. In the spectrum of dihydrofarfugin B (XV), obtained by hydrogenation (Pt, MeOH) of II, signals due to a primary methyl appear at δ 0.91 ppm (m, due to virtual couplings). An IR absorption band arising from <u>trans</u> -CH=CH- in II (965 cm^{-1}) disappears in the IR spectra of XII, XIV and XV.

The result of NOE experiments on XII (Table) favours II over II' for farfugin B. The structure II is more plausible than II' from biogenetic considerations, provided that I and II have a common precursor (XVI). Any furanoeremophilane-diol, -triol or their equivalents may be transformed biogenetically or chemically by elimination of oxygen functions (substituents, X and Y) into I and II or their derivatives as shown in schema.$^{8)}$ In literature, we can find out some furanoeremophilane derivatives, such as furanofukinol (XVII)$^{9)}$, euryopsol (XVIII)$^{10)}$ and kablicin (XIX)$^{11)}$, which fulfil the stereochemical requirements for such a transformation (cf. XVI, XVI', XVI''). In fact, we observed a facile transformation of furanoeremophilane-6β,10β-diol (XX)$^{12)}$ into I and II on dehydration with $POCl_3$.$^{13)}$ Thus, farfugin B should be represented by II. Studies on mechanism of this reaction is under way.



XVIII R = OH

XX R = H

XIX R = $CO-C(CH_3)=CHCH_3$

$R' = CO-CH=C(CH_3)_2$

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