Tetrahedron Letters No. 43, pp. 4007 - 4010, 1971. Pergamon Press. Printed in Great Britain.

NEW FURANOSESQUITERPENES FROM <u>LIGULARIA</u> <u>JAPONICA</u> LESS.
FURANOEREMOPHILANE-6β,10β-DIOL, 10β-HYDROXY-6β-METHOXYFURANOEREMOPHILANE AND 10β-HYDROXYFURANOEREMOPHILAN-6β-YL 2'ξ-METHYLBUTANOATE

Masahiro Tada, Yoshihiko Moriyama, Yoshiaki Tanahashi and Takeyoshi Takahashi
Department of Chemistry, Faculty of Science,
The University of Tokyo, Bunkyo-ku, Tokyo, Japan
and
Masaru Fukuyama and Kenichi Sato
Sagami Chemical Research Center, Ohnuma, Sagamihara-shi, Kanagawa, Japan

(Received in Japan 8 September 1971; received in UK for publication 22 September 1971)

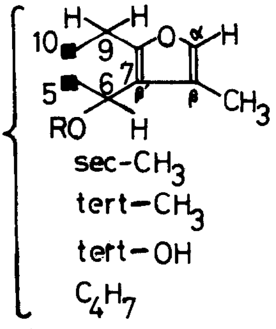
IN the course of chemical investigation on constituents of the genus <u>Ligularia</u> (Compositae), we have isolated three new furanosesquiterpenes from <u>Ligularia japonica</u> Less. We report here the evidence leading to structures of furanoeremophilane-6β,10β-diol (I), 10β-hydroxy-6β-methoxyfuranoeremophilane (II) and 10β-hydroxyfuranoeremophilan-6β-yl 2'ξ-methylbutanoate (III) for these substances.

The roots of plant were extracted with benzene followed by methanol. The molecular formula of $C_{15}H_{22}O_3$ (M^+ at m/e 250) was given for I, m.p. 122°, $[\alpha]_D$ + 58° (EtOH), isolated from the benzene extract. The IR (ν_{max} 3608, 3544, 3504, 1645, 1565 and 1080 cm^{-1}; in 0.005M soln. of CCl_4), UV (λ_{max} 215 nm, ε 8000 ; in EtOH) and PMR (in $CDCl_3$) spectra together with the positive Ehrlich test show the presence of a secondary Me (3H, δ 0.78 ppm, d, J = 5.5 Hz), a tertiary Me (3H, δ 1.22, s), two allylic protons (an AB-type quartet ; δ_A 3.21, d, and δ_B 2.53 d ; J = (-)17.8 ; $\blacksquare\!-\!C\underline{H}_2$-furan), a β-methyl-substituted (3H, δ 2.03, d, J = 1.5) furan with an α-proton (1H, δ 7.08, m), and of the OH group. In the PMR spectrum (in C_6H_6), on addition of D_2O, both of a doublet (1H, δ 2.72, J = 7.5 ; $-\overset{|}{C}H-O\underline{H}$) and a singlet (1H, δ 2.93 ; $-\overset{|}{\underset{|}{C}}-O\underline{H}$) disappear, while a doublet (1H, δ 4.41, J = 7.5 ; $\blacksquare-\overset{\blacksquare}{C}\underline{H}-OH$) changes into a singlet. Acetylation of I with Ac_2O in pyridine gave a monoacetate (IV), $C_{17}H_{24}O_4$ (M^+ at m/e 292), IR (ν_{max} 3560, 1740, 1640 and 1560 cm^{-1}; in CCl_4). The nature of three oxygen atoms involved in I is thus characterized, showing the presence of a secondary and a tertiary OH together with a furan.

An upfield shift of a signal due to the β-Me on furan ring by acetylation (Δ 0.12 ppm, in $CDCl_3$)$^{1)}$ indicates that the secondary hydroxyl-bearing carbon is attached to the another β-position (that is, to the β'-position ; C-7) of the furan ring for I. This received support from the nuclear Overhauser effects (NOE)$^{2)}$ observed between a proton (6-H) on acetoxyl-bearing carbon and a β-Me (11-Me) on the furan ring for IV (Table). These findings along with the observation that an NOE is observed between an α-proton (12-H) and a β-Me (11-Me) on the furan ring (Table), lead to the presence of a partial structure (A, R = H) for I. By means of biogenetic considerations, this structure can be extended to two alternative structures, B (R = H) and B' (R = H), for I.

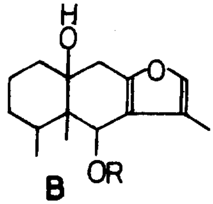
The substance (II), m.p. 82-84°, $C_{16}H_{24}O_3$ (M^+ at m/e 264), IR (ν_{max} 3488, 1634, 1560 and 1084 cm^{-1}; in 0.005M soln. of CCl_4) was isolated from the methanol extract. The same compound (II) was obtained by treatment of I with MeOH-AcOH or with $MeI-Ag_2O-HCONMe_2$, showing that a secondary OH of I was methylated to give II. This suggests that II would be an artifact produced by extraction with methanol. The presence of an NOE between a proton (6-H) on methoxyl-bearing

A

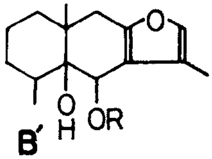


sec-CH_3
tert-CH_3
tert-OH
C_4H_7

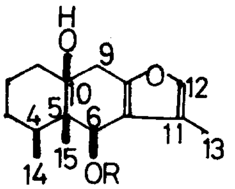
(■ indicates carbon with no proton)



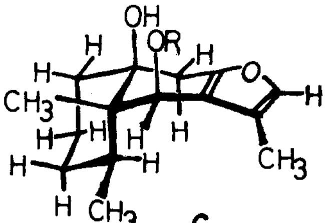
B



B'



I R = H
II R = CH_3
III $R = -\underset{O}{\overset{\|}{C}}-\underset{CH_3}{CH}-CH_2-CH_3$
IV R = Ac



C

TABLE PMR Spectral Data[a)]

Chemical shifts (δ, ppm downfield from TMS) and coupling constants (J, Hz)

Solvents	(I) C_6D_6	(II) CCl_4	(IV) C_6D_6
4-Me	$0.55\underline{A}_3B$	0.70d	$0.72\underline{A}_3B$
5-Me	1.11s	1.12s	1.04s
11-Me	1.95d	1.99d	1.89d
6-H	4.41d[b)]	4.05s	6.34s
9α-H	2.94d	3.01d	2.99d
9β-H	2.42d	2.59d	2.69d
12-H	7.00m	7.02m	6.94m
6-OH	2.72d[b)]		
6-OMe		3.28s	
6-OAc			1.50s
10-OH	2.93s[b)]	4.30s	3.22br

Nuclear Overhauser effects (increases in integrated signal intensities, %)

Observed protons	Saturated protons	NOE (I)	NOE (II)	NOE (IV)
6-H	4-Me			21
6-H	5-Me		13	
9α-H	5-Me	nil		nil
9β-H	5-Me	nil		nil
6-H	11-Me			4
12-H	11-Me	32		20

$J_{4,14} = 5.5$

$J_{6,6\text{-}O\underline{H}} = 7.5$

$J_{9\alpha,9\beta} = (-)17.8$

$J_{12,13} = 1.5$

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. NOE experiments were performed with sweep rates of 1 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 are ±0.01 ppm for chemical shifts, ±0.2 Hz for coupling constants, and about ±2 % for NOE values. b) measured in C_6H_6.

carbon and a tertiary Me (5-Me), and the absence of NOE between a tertiary Me (5-Me) and each of two allylic protons (9α- and 9β-H)(Table), imply that the tertiary Me is located on C-5 with an equatorial conformation. The IR spectrum of I indicates the presence of intramolecular hydrogen bond between two OH's. When I was treated with $NaIO_4$, no $NaIO_4$ was consumed ; this shows the absence in I of an α-glycol (especially, of an α-cis-glycol) system. The structure (B') with selinane (eudesmane) skeleton can therefore be excluded ; the diol (I) should be represented by B.*

The presence of intramolecular hydrogen bond mentioned above shows that a tertiary and a secondary OH (6-H) must be in 1,3-diaxial (that is, in cis) relationship to each other, and leads to the location of a tertiary OH on C-10 for I. A downfield shift (by 0.23 ppm) of a signal due to a tertiary Me (5-Me) of I

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* No other formulation, for example such as that involves a spiro, five- or seven-membered ring, is compatible with the observed data.

is observed when the solvent is replaced from $CDCl_3$ to C_5H_5N.3) The tertiary Me (5-Me) and the two OH's are therefore in cis relationships to one another. The corresponding downfield shift for II is relatively small (0.08 ppm); this could be interpreted by the strong intramolecular hydrogen bond which inhibits competitively the solute-solvent association.2) An NOE observed between a proton (6-H, equatorial) and a secondary Me shows that this secondary Me is located on C-4 with an equatorial conformation (that is, 6-OAc and 4-Me are in cis relationship to each other) for IV (Table).

These observations lead to the structure (I, or its mirror image) for the diol. The conformation of I is shown by C (R = H). The structures (II and IV ; or their mirror images) follow for the monomethyl ether and monoacetate, respectively.

These results received support from the induced paramagnetic shift experiments. The shift reagent, $Eu(dpm)_3$, associates more strongly with a hydroxyl than with an ether group.4) Both of the 5-Me and 9β-H shift largely for I and II. A very large shift is observed for the 6-H of I, while the smaller shift for the corresponding proton of II.

The benzene extract also gave III, m.p. ∼40°, $C_{20}H_{30}O_4$ (M^+ 334), IR (ν_{max} 3570, 3500, 1725, 1640 and 1565 cm^{-1}, in CCl_4). Treatment of III with $LiAlH_4$ yielded I. This suggests that III is an ester comprising from I and a carboxylic acid (C_4H_9COOH). In the PMR spectrum (in $CDCl_3$), there appear signals due to protons other than those of the structure moiety (I): a triplet at δ 0.88 ppm (3H, J = 5.5 Hz ; $C\underline{H}_3$-CH_2-), a doublet at δ 1.14 ppm (3H, J = 7 Hz ; $C\underline{H}_3$-CH-), and a multiplet at δ 2.34 ppm {1H, -O-CO-$C\underline{H}(CH_3)$-}. The ester must therefore be represented by III.

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