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STUDIES ON SESQUITERPENOIDS—IX[1]

STRUCTURE OF LIGULAROL AND LIGULARONE FROM *LIGULARIA SIBIRICA* CASS

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Abstract—Two crystalline sesquiterpenes having a furan ring, named ligularol and ligularone, have been isolated from *Ligularia sibirica* Cass. Ligularol and ligularone were characterized as 6β-hydroxyfuranoeremophilane (petasalbine) and 6-oxofuranoeremophilane, respectively.

INVESTIGATIONS reported in the literature on the components of *Ligularia* genus[2] (Compositae) are limited. The present paper deals with the isolation of ligularol and ligularone from *Ligularia sibirica* Cass. and the proof of their structures.

Ligularol (I) was obtained from the root of the plant as colourless prisms, $C_{15}H_{22}O_2$, m.p. 80 $\sim$ 81°, $[\alpha]_D$ −11·8°. From its UV (λ_{max} 220 mμ, ε 6580) and IR spectra (ν_{max} 1647 and 1568 cm^{-1}), and from its positive Ehrlich's colour test, the ligularol molecule is assumed to contain a furan ring. This is confirmed by its NMR spectrum: a methyl signal on a furan ring at 7·95 τ (doublet J = 1·1); one furan ring proton at 2·95 τ (quartet J = 1·1).

Its IR spectrum also shows a band at 3626 cm^{-1}, indicating the presence of an hydroxyl group. When ligularol (I) was treated with acetic anhydride–pyridine overnight at room temperature, it afforded a monoacetate (II) as colourless prisms, m.p. 54 $\sim$ 55°, which exhibits no hydroxyl band in its IR spectrum. These results indicate that one of the two oxygen atoms in I is present in a furan ring and the other in an hydroxyl group.

Hydrogenation of ligularol (I) in ethanol over Adams' catalyst yielded tetrahydroligularol (III) as colourless plates, $C_{15}H_{26}O_2$, m.p. 99 $\sim$ 100°. When the catalytic hydrogenation was carried out in acetic acid, a mixture of hydrogenolytic compounds (V and VI) and tetrahydroligularol acetate (IV), colourless plates, $C_{17}H_{28}O_3$, m.p. 95 $\sim$ 96°, was obtained. Since one of the hydrogenolytic products (V), a colourless oil, $C_{15}H_{28}$, was identified as the known eremophilane[3] by comparison of their IR spectra,[4] the eremophilane skeleton of ligularol is established.

The position of the oxygen functions in ligularol (I) was proved by structure elucidation of its dehydro compound (VII). Oxidation of I with chromium trioxide

[1] Part VIII: H. Minato, S. Nosaka and I. Horibe, *J. Chem. Soc.* 5503 (1964).
[2] J. Shimoyama and G. Aikawa, *Yakugaku Zasshi* **6**, 104 (1891); Y. Asahina, *Ibid.* **28**, 811 (1913).
[3] L. Novotný, J. Jizba, V. Herout, F. Šorm, L. H. Zalkow, S. Hu and C. Djerassi, *Tetrahedron* **19**, 1101 (1963).
[4] M. Horák, O. Motl, J. Plíva and F. Šorm, *Terpenspektren* II S I 18 Akademie Verlag, Berlin (1963).

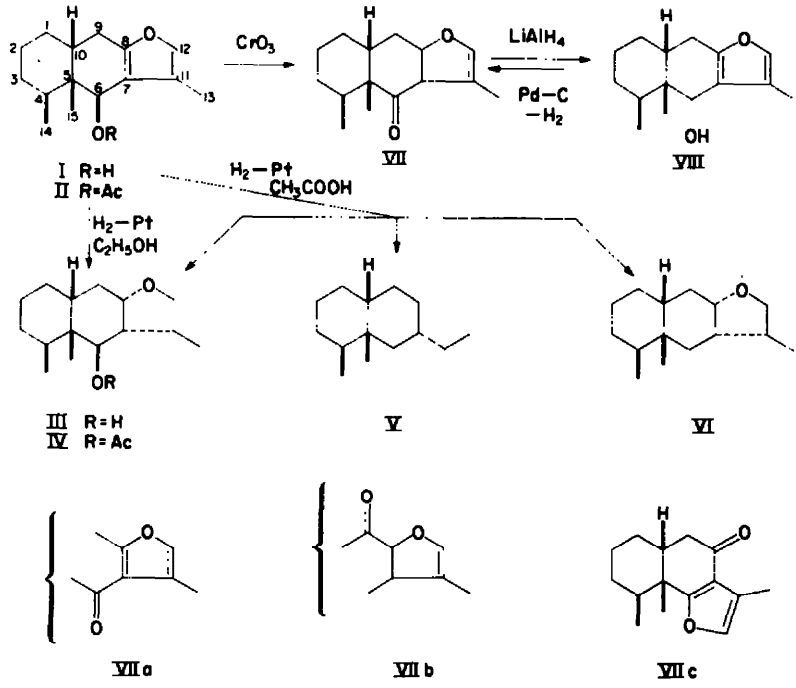


Chart I

in pyridine gave the ketone VII which is identical with ligularone, a main furano compound isolated from the aerial part of the same plant.

Ligularone (VII) was crystallized from petroleum ether as colourless plates, $C_{15}H_{20}O_2$, m.p. 64 ~ 65°, $[\alpha]_D$ −57·7°. It shows characteristics of a furan ring in its IR, NMR spectra and Ehrlich's colour test. Ligularone also exhibits an IR band at 1668 cm^{-1} indicating the conjugation of its carbonyl group with the furan ring. In order to determine which of the partial structures VIIa and VIIb should be assigned to ligularone, its dipole moment was measured. The observed value of 2·55 D is in good agreement with a calculated moment of 2·35 D for VIIa* and differs from that of 3·66 D for VIIb,* excluding the formula VIIb. The UV spectral maximum at 269 mμ (ε 3260)[7] of ligularone also supports this conclusion. Hence the structures VII and VIIc are taken in account for ligularone.

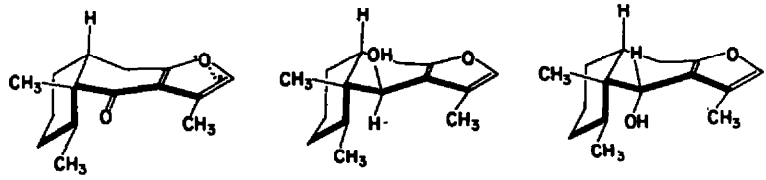
Reduction of ligularone with LAH afforded epiligularol (VIII) as colourless prisms, $C_{15}H_{22}O_2$, m.p. 67 ~ 68°, acetylation of which was unsuccessful under the same condition as described for ligularol (I). Dehydrogenation of VIII with 10%

* Each of the calculated moments was obtained as a vector sum of group moments. Assuming that the furan ring has a regular pentagon form, and that the carbonyl group is in the plane of the furan ring and parallel to one of the double bonds, one can calculate these moments from the observed moment of methyl vinyl ketone, 3·0 D,[5] and that of the furan ring, 0·69 D.[6]

[5] C. P. Smith, *Dielectric Behavior and Structure* p. 290 McGraw-Hill, New York (1955).
[6] Ref 5, p. 299.
[7] H. Sttetter and R. Lauterbach, *Chem. Ber.* **93**, 603 (1960).

Pd–C led to regeneration of ligularone. This fact, together with the NMR data of VIII (a singlet one proton signal at 5·69 τ), suggests that both carbon atoms adjacent to the carbon bearing an hydroxyl group have no hydrogen atoms available for dehydrogenation. If ligularone contains structure VIIc, dehydrogenation of epiligularol would not produce ligularone but further unsaturated compounds. It follows therefore that ligularone is 6-oxofuranoeremophilane (VII), and ligularol and epiligularol are 6-hydroxyfuranoeremophilanes (I and VIII).

Eremophilane (V) was obtained by hydrogenation of ligularol and the stereochemistry of V and its derivatives have been elucidated by Novotný *et al.*,[3] so that ligularone should be represented by formula IX, and ligularol and epiligularol by formulas X and XI (*vice versa*), respectively.



IX X XI

Chart 2

Table 1 summarizes the NMR spectral data of the furano compounds obtained in the present work.

From the following observations (a, b and c), 6β-hydroxyfuranoeremophilane (X) is assigned to ligularol and 6α-hydroxyfuranoeremophilane (XI) to epiligularol: (a) The signal of 14-methyl group in epiligularol appears in a lower field than that in

TABLE 1. NMR DATA (τ)

	13-CH_3	14-CH_3	15-CH_3	6-H	12-H
Ligularone (IX)	7·80 d (1·2)†	9·12 d (6·9)	8·88 s	—	2·94 q (1·2)
Ligularol (X)	7·95 d (1·1)	9·12 d (6·1)	9·00 s	5·30 s	2·95 q (1·1)
Ligularol acetate	8·09 d (1·2)	9·12 d (6·0)	9·05 s	3·82 s	2·95 q (1·2)
Epiligularol (XI)	7·96 d (1·2)	8·96 d (6·9)	9·12 s	5·69 s	2·92 q (1·2)

† s = singlet, d = doublet, q = quartet; apparent coupling constants (c/s) are shown in parentheses.

ligularol, indicating that the methyl group at C-4 and the hydroxyl at C-6 in epiligularol are present in a 1,3-diaxial-like relationship.[8] (b) The signal of 14-methyl group in ligularol does not shift when ligularol is changed into its acetate.[8] (c) Epiligularol failed to acetylate as mentioned above, which fact is attributed to steric interactions between the hydroxyl group and the three methyl groups as shown in formula XI.

Incidentally, Šorm *et al.*[9] gave the structure 6ξ-hydroxyfuranoeremophilane for

[8] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, *Chem. Pharm. Bull.* **10**, 338 (1962).

[9] L. Novotný, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **29**, 2189 (1964).

petasalbine, and the physical constants of ligularol are in excellent agreement with those of petasalbine. Ligularol proved to be identical with an authentic sample of petasalbine* by mixed m.p. determination and by comparison of their IR spectra. Therefore, the term of ligularol must be removed from the literature.

EXPERIMENTAL

NMR spectra were recorded on a Varian A-60 NMR Spectrometer in $CDCl_3$ solutions. All m.ps were measured on a Kofler block and are uncorrected. UV spectra were taken in 95% EtOH and rotations in $CHCl_3$.

Isolation of ligularol (I) *from the root of the plant*

The dried and sliced root of *Ligularia sibirica* Cass. (2·9 kg) was extracted with ether (14 l. × 3) at room temp for 3 days. The ether extract (150 g) was again dissolved in ether (3 l.), washed with 10% Na_2CO_3aq, dried (Na_2SO_4) and evaporated *in vacuo* to give a dark brown residue (128 g). The residue was extracted with pet. ether (1 l.) and the pet. ether solution evaporated *in vacuo* to yield a reddish-brown oil (114 g). This pet. ether extract (14·5 g) was fractionated by distillation into 3 portions, a pale yellow oil of b.p. 92 ~ 127°/1·5 mm (A, 1·84 g), a yellow viscous oil of b.p. 127 ~ 139°/1·5 mm (B, 6·14 g), and a reddish-brown distillation residue (C, 6·33 g). The oil B was dissolved in pet. ether and left overnight in a refrigerator giving I (1·24 g) as colourless prisms, m.p. 80 ~ 81°. The mother liquor was chromotagraphed on alumina (Merck III, neutral, 150 g). Elution with pet. ether–ether (9:1) afforded a pale yellow oil (3·98 g), which was crystallized from pet. ether to give I (1·82 g) as colourless prisms, m.p. 80 ~ 81°, $[\alpha]_D^{24}$ −11·8° (±2°) (*c*, 0·846), λ_{max} 220 mμ (ε 6580), $\nu_{max}^{CHCl_3}$ 3626, 1647 and 1568 cm^{-1}. (Found: C, 76·84; H, 9·45. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%.) This is identical with petasalbine provided from Prof. Šorm by mixed m.p. determination and comparison of IR spectra.

Acetylation of ligularol (I) *with acetic anhydride–pyridine*

To a solution of ligularol (I, 30 mg) in pyridine (0·5 ml), acetic anhydrine (0·4 ml) was added. The mixture was allowed to stand overnight at room temp and yielded ligularol acetate (II) as colourless prisms (from pet. ether), m.p. 54 ~ 55°, $\nu_{max}^{CCl_4}$ 1734, 1646, 1566 and 1240 cm^{-1}. (Found: C, 73·79; H, 8·85. $C_{17}H_{24}O_3$ requires: C, 73·88; 8·75%.)

Catalytic hydrogenation of ligularol (I) *over Adams' catalyst*

(a) A mixture of Adams' catalyst (120 mg) and ligularol (I, 685 mg) in EtOH (20 ml) was reduced catalytically at room temp. When 120 ml H_2 had been absorbed, the uptake of H_2 ceased. After removal of the catalyst and solvent, the residue (729 mg) was chromatographed on alumina (Merck III, neutral, 25 g). The crystalline substance (549 mg) obtained from the eluates with pet. ether–benzene (9:1), (4:1) and (1:1) was recrystallized from pet. ether to give III (270 mg) as colourless plates, m.p. 99 ~ 100°, $[\alpha]_D^{24}$ +49·2° (±2°) (*c*, 1·020), $\nu_{max}^{CCl_4}$ 3642 and 3462 cm^{-1}. (Found: C, 75·63; H, 11·14. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%.)

Compound III (30 mg) was acetylated with acetyl chloride (0·5 ml) and pyridine (1 ml) in a usual manner. Ice water was added to the reaction mixture, and the ether extract was washed and dried (Na_2SO_4). The residue was dissolved in ether and chromatographed on alumina (Merck II, neutral). The crystalline substance thus obtained was recrystallized from pet. ether to give IV as colourless plates, m.p. 95 ~ 96°, $\nu_{max}^{CCl_4}$ 1731 and 1235 cm^{-1}. (Found: C, 72·93; H, 10·27. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%.)

(b) A mixture of Adams' catalyst (350 mg) and I (1·99 g) in acetic acid (20 ml) was reduced catalytically at room temp. When 625 ml H_2 had been absorbed, the reaction stopped, and the catalyst and the solvent were removed. The residue was dissolved in ether and the ether solution washed with

* The authors express their deep gratitude to Professor F. Šorm of Institute of Organic Chemistry and Biochemistry, Czechoslovak Acadamy of Science, for his kind gift of the sample.

5% Na_2CO_3aq, dried (Na_2SO_4), and evaporated leaving a colourless oil (1·81 g), which was chromatographed on alumina (Merck I, neutral, 250 g). Elution with pet. ether and pet. ether–ether (9:1) afforded V (30 mg) as a colourless oil. (Found: C, 86·36; H. 13·60. $C_{15}H_{28}$ requires: C, 86·46; H, 13·54%), IR of which is identical with that of eremophilane.[4] Further elution with pet. ether–ether (4:1) and (1:1) afforded a pale yellow oil (722 mg) containing VI and IV, which was again chromatographed on alumina (Merck II, neutral, 30 g). The first elution with pet. ether–ether (9:1) afforded VI (498 mg) as a colourless mobile oil, b.p. 88 ~ 90°/1 mm (bath temp.), $[\alpha]_D^{25.5}$ +19·9° (±2°) (*c*, 0·927) (Found: C, 81·18; H, 11·71. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%) which had not an hydroxyl group in its IR. Further elution with pet. ether–ether (9:1) and (4:1) (210 mg) yielded IV as colourless plates, m.p. 95 ~ 96°, which is identical with IV obtained from III by mixed m.p. determination and comparison of IR spectra.

Oxidation of ligularol (I) *with chromium trioxide in pyridine*

To a solution of ligularol (360 mg) in pyridine (5 ml) was added a CrO_3–pyridine complex (300 mg in 10 ml), and the mixture was allowed to stand at room temp for 2 hr. Water was added to the mixture, and the ether extract was washed with 5% HCl, dried (Na_2SO_4) and evaporated leaving a pale yellow oil (314 mg). This was chromatographed on alumina (Merck III, neutral, 10 g) and elution with pet. ether afforded a crystalline substance (169 mg), which was recrystallized from pet. ether to give VII (73 mg) as colourless plates, m.p. 64 ~ 65°. This is identical with ligularone (*vide infra*) obtained from the aerial part of the plant by mixed m.p. determination and comparison of IR spectra.

Isolation of ligularone (VII) *from the aerial part of the plant*

The dried and sliced leaves and stems of *Ligularia sibirica* Cass (1·6 kg) were extracted with ether (20 l. × 3) at room temp for 3 days. The ether extract (73 g) was again dissolved in ether (2 l.), washed with 10% Na_2CO_3aq, dried (Na_2SO_4), and evaporated *in vacuo* to give a dark brown residue (62·5 g). The residue was extracted with 90% MeOH (800 ml) and the extract was evaporated *in vacuo* leaving a reddish-brown residue (36·5 g). The residue (34·5 g) was fractionated by distillation under red. press. as shown in Table 2. The fractions 4 ~ 6 (12·26 g) were combined and again distilled under

TABLE 2

Fraction	B.p., °C/mm	W. g
1	84 ~ 109/1	4·03
2	109 ~ 120/1	4·37
3	120 ~ 131/1	8·54
4	131 ~ 142/1	5·30
5	142 ~ 144/1	2·28
6	130 ~ 158/0·1	4·68
7	residue	4·88

red. press. to divide into 4 portions, an oil of b.p. 117 ~ 123°/0·3 mm (D, 4·28 g), an oil of b.p. 123 ~ 144°/0·3 mm (E, 3·07 g), an oil of b.p. 144 ~ 149°/0·3 mm (F, 2·04 g) and a distillation residue (G. 2·85 g). The oil D (3·30 g) was chromatographed on silica gel (Merck, 0·2 ~ 0·5 mm, 70 g). The crystalline substance (691 mg) obtained from the eluate with pet. ether–benzene (9:1) was recrystallized from pet. ether to give VII (359 mg) as colourless plates, m.p. 64 ~ 65°, $[\alpha]_D^{27}$ −57·7° (±2°) (*c*, 0·940), μ 2·55 D (25°, benzene), λ_{max} 269 mμ (ϵ 3240), $\nu_{max}^{CHCl_3}$ 1668, 1614 and 1568 cm^{-1}. (Found: C, 77·56; H, 8·92: $C_{15}H_{20}O_2$ requires: C, 77·56; H, 8·68%.)

Reduction of ligularone (VII) *with lithium aluminum hydride*

A solution of VII (100 mg) in dry ether (8 ml) was added dropwise to a suspension of LAH (20 mg) in dry ether (10 ml) with stirring in N_2 atm and stirred for 30 min at room temp. The mixture was decomposed by addition of water and 5% HCl, extracted with ether, washed with 2% $NaHCO_3$aq, dried (Na_2SO_4) and evaporated leaving a crystalline substance (93 mg). This was recrystallized from

pet. ether to give VIII (58 mg) as colourless prisms, m.p. 67 ~ 68°, $[\alpha]_D^{25}$ −7·2° (±2°) (*c*, 0·977), ν_{max}^{Nujol} 3438, 1650 and 1573 cm^{-1}. (Found: C, 76·68; H, 9·60. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%.)

Dehydrogenation of epiligularol (VIII)

A mixture of VIII (50 mg) and 10% Pd–C (50 mg) was heated at 310 ~ 315° (bath temp) for 2 min. The residue was extracted with pet. ether and the extract (33 mg) was separated by thin layer chromatography (20 × 20 cm × 0·75 mm Kieselgel GF plate; benzene). Compound VII (R_f 0·80, 21 mg) was extracted with ether. This is identical with VII by mixed m.p. determination and comparison of IR spectra.

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