New Eremophilane-Type Lactones from Ligularia Fauriei (Fr.) Koidz.

The structures of three new sesquiterpenes isolated from Ligularia Fauriei (Fr.) Koidz. were shown to be 1, 2, and 3, respectively.

In connection with structural studies on constituents of plants of the genus Ligularia (Compositae) and related plants,1) three new sesquiterpenes have been isolated from the benzene extract of Ligularia Fauriei (Fr.) Koidz. We wish to describe the structure determination leading to 1, 2, and 3 for these substances.

The molecular formula of $C_{15}H_{22}O_6$ was given for a compound (1), mp 217–218° (dec.), $[a]_D +82°$ ($c=0.98$, EtOH). The presence of an $\alpha,\beta$-unsaturated $\gamma$-lactone moiety4,5 and hydroxyl group(s) was suggested from the infrared (IR) ($\nu_{\text{max}}$ 3480, 3230, and 1721 cm$^{-1}$) and the ultraviolet (UV) ($\lambda_{\text{max}}$ 221 nm, $\epsilon$ 11800) spectra. The proton magnetic resonance (PMR) spectrum (acetone-$d_6$) showed the presence of a secondary methyl ($\delta$ 0.80, $d$-like; $C_{(4)}$–CH$_3$), a tertiary methyl ($\delta$ 1.12, s, $C_{(1)}$–CH$_3$), an olefinic methyl ($\delta$ 1.83, s, $C_{(1)}$–CH$_3$), and a proton ($\delta$ 4.64, br. s, $C_{(8)}$–H) attached to a carbon bearing an oxygen atom. Acetylation of 1 with acetic anhydride in pyridine yielded a diacetate (4), mp 120.5–121°, $C_{19}H_{26}O_8$ which gave no hydroxyl absorption in its IR spectrum. In the PMR spectrum (CDCl$_3$) of 4 two methyl signals newly appeared ($\delta$ 1.98, s, and $\delta$ 2.02, s, each CH$_2$CO–O–). Therefore two hydroxyl groups must be present in 1.

Reduction of 1 with sodium borohydride in methanol gave two products (5 and 6). The more polar product (5) [mp 208–207.5°, $[a]_D +213°$ ($c=1.19$, CHCl$_3$), $C_{15}H_{22}O_6$ (M$^+$ at m/e 250); $\nu_{\text{max}}$ 3440, 1739, 1709(sh), and 1690(sh) cm$^{-1}$; $\delta_{\text{max}}$ 218 nm, $\epsilon$ 14400; PMR (CDCl$_3$): $\delta$ 0.80 ($d$-like; $C_{(4)}$–CH$_3$), $\delta$ 1.13 (s, $C_{(1)}$–CH$_3$), $\delta$ 1.85 (d, $J_{6,13}=2$ Hz; $C_{(1)}$–CH$_3$), $\delta$ 4.80 (s, $C_{(8)}$–H), $\delta$ ca. 5.1 ($C_{(9)}$–H), and $\delta$ 2.25 (s, OH, disappeared on addition of D$_2$O); (acetone-$d_6$): $\delta$ 0.75 ($d$-like; $C_{(4)}$–CH$_3$), $\delta$ 1.10 (s, $C_{(1)}$–CH$_3$), $\delta$ 1.77 (d, $J_{6,13}=2$ Hz; $C_{(1)}$–CH$_3$), $\delta$ 4.70 (s, $C_{(8)}$–H), and $\delta$ ca. 5.1 ($C_{(9)}$–H)] proposed to be identical (mp, mixed mp, $[a]_D$, IR, UV, PMR, and mass spectra) with 6$\beta$-hydroxyeremophil-7(11)-en-12,8-$\alpha$-oxide (5).5–7 The less polar product (6) [mp 107–111°, $C_{15}H_{22}O_2$ (M$^+$ at m/e 234); $\nu_{\text{max}}$ 1734, 1670, and 1025 cm$^{-1}$; PMR (CDCl$_3$): $\delta$ 0.80 ($d$-like; $C_{(4)}$–CH$_3$), $\delta$ 1.05 (s, $C_{(1)}$–CH$_3$), $\delta$ 1.80 (d, $J_{6,13}=2$ Hz; $C_{(1)}$–CH$_3$), $\delta$ ca. 2.9 (d, $J=15$ Hz; an A-part of an AB-type quartet due to the allylic methylene protons at $C_{(6)}$),8 and $\delta$ 4.61 (m, $C_{(8)}$–H)] was found to be identical with eremophil-7(11)-en-12,8-$\alpha$-oxide (6).5,9 Similar reduction of 5 with sodium borohydride gave 6. The structure of 1 must contain one hydroxyl group more than that of 5.

In the PMR spectrum of 5 a multiplet due to a proton at $C_{(8)}$ appeared at $\delta$ ca. 5.1, while the corresponding signals were absent in that of 1. The presence in 5 of long-range spin-
coupling (2 Hz) of the C(8)-H to the olefinic C(11)-CH₃ protons (δ 1.85) was shown by proton magnetic double resonance (PMDR) experiments. The other spectral data of 1 and 5 were almost identical. These observations led to the location of an extra hydroxyl group on C(8) for 1.¹⁰ The structure of 1 should be represented by 6β, 8β-dihydroxyeremophil-7(11)-ene-12,8α-olide (1).

The compound (2), mp 253.5—254°, [α]D + 94° (c= 0.88, CHCl₃), C₁₆H₁₅O₆ (M⁺ at m/e 278), showed the IR (νmax 3260, 1787, and 1710 cm⁻¹) and the UV (λmax 214 nm, ε 12400) spectra suggesting the presence of an α,β-unsaturated γ-lactone and a γ-lactone moiety along with a hydroxyl group. The PMR spectrum (acetone-d₆) indicated the presence of a tertiary methyl (δ 1.28, s, C(5)-CH₃), an olefinic methyl (δ 1.86, d, J₆₅,1₃=2 Hz; C(11)-CH₃), a proton (δ 5.18, q, J₆₅,1₃=2 Hz; C(8)-H), and a hydroxyl group (δ 5.61, s, disappeared on addition of D₂O); signals due to a secondary methyl were absent. On acetylation with acetic anhydride in pyridine 2 gave a monoacetate (7), mp 183—184°, C₁₁H₂₀O₆ (M⁺ at m/e 320), which showed no hydroxyl absorption in its IR spectrum.

These spectral data could be best interpreted on the basis of the structure (2), providing that 2 belongs to a sesquiterpene of eremophilane-type. This received support from the following evidences. (i) Treatment of furanoeremophil-14β,6α-olide (8)¹¹ in dioxane with dicyanodichlorobenzocouquinone (DDQ)¹² at 80° for 1 hr yielded an unstable unsaturated enol lactone (9) [an amorphous compound, C₁₃H₁₀O₄ (M⁺ at m/e 260); νmax 1785 and 1665 cm⁻¹, Jmax 280 nm;³³] PMR (CDCl₃); δ 1.38 (s, C(5)-CH₃), δ 2.12 (br. s, C(14)-CH₂), δ 3.26 (dd, J=2 and 12 Hz; C(4)-H), δ 2.96 (m, C(10)-H), δ 5.28 (q, J₆₅,1₃=1.5 Hz; C(9)-H), and δ 5.65 (d, J₆₅,1₃=3 Hz; C(8)-H). The same compound (9) was obtained by dehydration of 2 with phosphorus oxychloride in pyridine (identification: IR, PMR, and mass spectra). (ii) The lactone (8) in methanol was irradiated with a high pressure mercury lamp under an oxygen atmosphere for 1 hr in the presence of Rose Bengal to afford a compound identical (mp, mixed mp, IR and PMR spectra) with 2. These observations led to the structure of 8β-hydroxyeremophil-7(11)-ene-12, 8α; 14β, 6α-diolide (2)¹⁴,¹⁵ for 2.

The presence of an α,β-unsaturated γ-lactone and a γ-lactone grouping was suggested for the compound (3) [mp 186—186.5° (decomp.), [α]D + 93° (c=0.91, CHCl₃), C₁₅H₁₅O₄ (M⁺ at m/e 262); νmax 1786, 1739, and 1684 cm⁻¹; Jmax 217 nm (ε 19300); PMR (CDCl₃); δ 1.29 (s, C(5)-CH₃), δ 2.00 (t, J₆₅,1₃=2 Hz; J₆₅,1₃=2 Hz; C(11)-CH₃), δ 4.75 (m, C(8)-H), δ 5.05 (br. s, C(9)-H)].

¹⁰ An alternative structure with 8α-OH configuration would show a different PMR spectrum from that of 5 (with 8β-H configuration).
¹² Oxidation of atracylone and lindene with DDQ has been described: K. Takeda, M. Ikuta, M. Miyawaki, and K. Tori, Tetrahedron, 22, 1159 (1966).
¹³ The ε value could not be determined precisely due to fragility of the compound.
¹⁴ Closely related PMR spectral data for 1, 2, 3, 5, and 6, suggested that the configurations at C(8) of these compounds are the same (C(8)-H or C(8)-OH). PMDR experiments showed the presence of long-range spin-couplings of the olefinic C(11)-CH₃ protons to the C(8)-H (at δ 5.18 for 2 and at δ 5.05 for 3) and to the C(8)-H (at δ 4.75 for 3).
¹⁵ The lactones (2 and 1) might be considered as artifacts produced, during isolation, from 8 and 6β-hydroxyfuranoeremophilane, respectively. An examination on this point is under way.
C\(_{(\text{aq})-\text{H}}\). Reduction of 2 with sodium borohydride in methanol yielded 3. The structure of 3 must be shown as eremophil-7(11)-ene-12,8\(\alpha\); 14\(\beta\),6\(\alpha\)-diolide (3),\(^4\) since 1 was reduced with sodium borohydride to form 5 with a loss of the hydroxyl group at C(6\(\beta\)). The spectral data described above are compatible with the structure (3).

Finally, 6\(\beta\)-hydroxyeremophil-7(11)-ene-12,8\(\alpha\)-olide (5)\(^5\)-\(^7\) was also isolated from the same plant.

Compounds 2 and 3 constitute the first examples of eremophilane-type sesquiterpenes having two lactone rings in their molecules.

**Acknowledgement** We wish to thank Dr. H. Ishii, Shionogi Research Laboratory, Osaka, for a generous gift of an authentic sample of 6\(\beta\)-hydroxyeremophil-7(11)-ene-12,8\(\alpha\)-olide (5).

Department of Chemistry, Faculty of Science, The University of Tokyo, Bunkyo-ku, Tokyo

Yoshishiko Moriyama
Takeyoshi Takahashi

Received September 13, 1975

---

**Opening of the Cephalosporin Dihydrothiazine Ring**

2-Ethoxy-3-cephem-1\(\beta\)-oxide (3) was found to be thermally unstable and easily converted into isothiazolones (4, 5, 6, 9, 10), and the \(\beta\)-lactam derivative (8) under varying reaction conditions. Furthermore, 2-ethoxy-3-cephem (2) was treated with tert-butyl hypochlorite, giving the azetidinone-oxazoline acetate (14).

In a previous paper,\(^1\) we described a new rearrangement reaction of 2-methylthiio- or 2-methoxyccephalosporins into azlactone derivatives similar to the penicillin-penicillenate rearrangement reaction.\(^2\) This reaction suggested that introduction of a heteroatom substituent at C(2) of cepham molecules would facilitate ring opening of the dihydrothiazine moiety. Further, we wish to add herein other transformation reactions of 2-alkoxycephem involving S(1)–C(2) bond fission.

**Treatment of methyl 7\(\beta\)-benzamido-3-methyl-3-cephem-4-carboxylate**\(^3\) (1) with 1.2 equivalents of tert-butyl hypochlorite in ethanol-containing methylene chloride (0\(^\circ\), 1 day, 45\% yield) gave a 2\(\alpha\)-ethoxy-3-cephem (2, mp 178–179.5\(^\circ\)).\(^4\) Successive oxidation of 2 with 1 equivalent of *meta*-chloroperbenzoic acid in chloroform (0\(^\circ\), 1 hr, 73\% yield) afforded a 2\(\alpha\)-ethoxy-1\(\beta\)-oxide [3, mp 137–138\(^\circ\); IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3320, 1785, 1736, 1660, 1543; NMR (CDCl\(_3\)) \(\delta\) ppm: 1.20 (3\(H\), t, \(J=7.0\), –OCH\(_3\)CH\(_3\)), 2.12 (3\(H\), s, 3-CH\(_3\)), 3.80 (3\(H\), s, –COOCH\(_3\)), 4.60 (1\(H\), d, \(J=5.5\), H-6), 4.63 (1\(H\), d, H-2), 6.25 (1\(H\), dd, \(J=5.5\) and 10, H-7)]. The 2\(\alpha\)-ethoxy-1-oxide 3 thereby obtained was found to be thermally unstable in protic solvents; and 3 was easily converted into an isothiazolone diethylacetal [4, mp 142–143\(^\circ\); IR \(\nu_{\text{CH}}\) cm\(^{-1}\): 3430, 1734, 1660, 1524;]

---

4) All compounds were characterized by infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry and also by elementary analysis.