Communications to the Editor

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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 $C_{15}H_{22}O_4$[2,3] was given for a compound (**1**), mp 217—218° (dec.), $[\alpha]_D$ $+82°$ ($c=0.98$, EtOH). The presence of an α,β-unsaturated γ-lactone moiety[4,5] and hydroxyl group(s) was suggested from the infrared (IR) (ν_{max}^{Nujol} 3480, 3230, and 1721 cm^{-1}) and the ultraviolet (UV) (λ_{max}^{EtOH} 219 nm, ε 11800) spectra. The proton magnetic resonance (PMR) spectrum (acetone-d_6) showed the presence of a secondary methyl (δ 0.80, *d*-like; $C_{(4)}$-CH_3), a tertiary methyl (δ 1.12, s, $C_{(5)}$-CH_3), an olefinic methyl (δ 1.83, s, $C_{(11)}$-CH_3), and a proton (δ 4.64, br. s, $C_{(6\alpha)}$-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°, $C_{19}H_{26}O_6$,[2] which gave no hydroxyl absorption in its IR spectrum. In the PMR spectrum ($CDCl_3$) of **4** two methyl signals newly appeared (δ 1.98, s, and δ 2.02, s, each $\underline{CH_3}CO$-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 207—207.5°, $[\alpha]_D$ $+213°$ ($c=1.19$, $CHCl_3$), $C_{15}H_{22}O_3$ (M^+ at *m/e* 250); ν_{max}^{Nujol} 3440, 1739, 1709(sh), and 1690(sh) cm^{-1}; λ_{max}^{EtOH} 218 nm, ε 14400; PMR ($CDCl_3$): δ 0.80 (*d*-like; $C_{(4)}$-CH_3), δ 1.13 (s, $C_{(5)}$-CH_3), δ 1.85 (d, $J_{8\beta,13}=2$ Hz; $C_{(11)}$-CH_3), δ 4.80 (s, $C_{(6\alpha)}$-H), δ *ca.* 5.1 (m, $C_{(8\beta)}$-H), and δ 2.23 (s, OH, disappeared on addition of D_2O); (acetone-d_6): δ 0.78 (*d*-like; $C_{(4)}$-CH_3), δ 1.10 (s, $C_{(5)}$-CH_3), δ 1.77 (d, $J_{8\beta,13}=2$ Hz; $C_{(11)}$-CH_3), δ 4.70 (s, $C_{(6\alpha)}$-H), and δ *ca.* 5.1 (m, $C_{(8\beta)}$-H)] proved to be identical (mp, mixed mp, $[\alpha]_D$, IR, UV, PMR, and mass spectra) with 6β-hydroxyeremophil-7(11)-en-12,8α-olide (**5**).[5-7] The less polar product (**6**) [mp 107—111°, $C_{15}H_{22}O_2$ (M^+ at *m/e* 234); ν_{max}^{Nujol} 1734, 1670, and 1025 cm^{-1}; PMR ($CDCl_3$): δ 0.80 (*d*-like; $C_{(4)}$-CH_3), δ 1.05 (s, $C_{(5)}$-CH_3), δ 1.80 (d, $J_{8\beta,13}=2$ Hz; $C_{(11)}$-CH_3), δ *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 δ 4.61 (m, $C_{(8\beta)}$-H)] was found to be identical with eremophil-7(11)-en-12,8α-olide (**6**).[7,9] 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 $C_{(8\beta)}$ appeared at δ *ca.* 5.1, while the corresponding signals were absent in that of **1**. The presence in **5** of long-range spin-

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[1] T. Sato, Y. Moriyama, H. Nagano, Y. Tanahashi, and T. Takahashi, *Bull. Chem. Soc. Japan*, 48, 112 (1975). And the references cited therein.

[2] Elemental analysis of the compound gave a satisfactory result.

[3] The mass spectrum of **1** showed the M-18 ion peak at *m/e* 248, while no molecular ion peak was observed.

[4] K. Takeda, H. Minato, M. Ishikawa, and M. Miyawaki, *Tetrahedron*, 20, 2655 (1964).

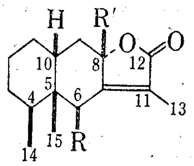
[5] H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc.* (*C*), **1966**, 1545.

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

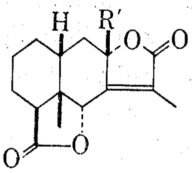
[7] The $C_{(8\beta)}$-H configuration of **5** was determined by X-ray study: C. Kabuto, N. Takada, S. Maeda, and Y. Kitahara, *Chem. Lett.*, **1973**, 371.

[8] The B-part signals were overlapped with other signals.

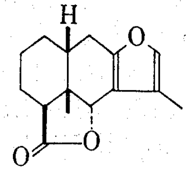
[9] L. Novotný, J. Jizba, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 27, 1393 (1962); M. Horák, O. Motl, J. Plíva, and F. Šorm, "Die Terpene," Teil II, S I 28, Akademie-Verlag, Berlin, 1963.



1 R=OH, R'=OH
4 R=OAc, R'=OAc
5 R=OH, R'=H
6 R=H, R'=H



2 R'=OH
3 R'=H
7 R'=OAc



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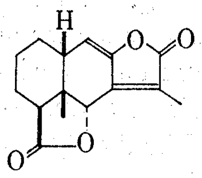

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coupling (2 Hz) of the $C_{(8\beta)}$–H to the olefinic $C_{(11)}$–CH_3 protons (δ 1.85) was shown by proton magnetic double resonance (PMDR) experiments. The other spectral data of **1** and **5** were almost identical. These observations led to the location of an extra hydroxyl group on $C_{(8\beta)}$ for **1**.[10] The structure of **1** should be represented by 6β, 8β-dihydroxyeremophil-7(11)-en-12,8α-olide (**1**).

The compound (**2**), mp 253.5—254°, $[\alpha]_D$ +94° (c=0.88, $CHCl_3$), $C_{15}H_{18}O_5$[2] (M^+ at m/e 278), showed the IR (ν_{max}^{Nujol} 3260, 1787, and 1710 cm^{-1}) and the UV (λ_{max}^{EtOH} 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-d_6) indicated the presence of a tertiary methyl (δ 1.28, s, $C_{(5)}$–CH_3), an olefinic methyl (δ 1.86, d, $J_{6\beta,13}$=2 Hz; $C_{(11)}$–CH_3), a proton (δ 5.18, q, $J_{6\beta,13}$=2 Hz; $C_{(6\beta)}$–H), and a hydroxyl group (δ 6.51, s, disappeared on addition of D_2O); signals due to a secondary methyl were absent. On acetylation with acetic anhydride in pyridine **2** gave a monoacetate (**7**), mp 183—184°, $C_{17}H_{20}O_6$[2] (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 furanoeremophilan-14β,6α-olide (**8**)[11] in dioxane with dicyanodichlorobenzoquinone (DDQ)[12] at 80° for 1 hr yielded an unstable unsaturated enol lactone (**9**) [an amorphous compound, $C_{15}H_{16}O_4$ (M^+ at m/e 260); ν_{max}^{neat} 1785 and 1665 cm^{-1}, λ_{max}^{EtOH} 280 nm;[13] PMR ($CDCl_3$); δ 1.38 (s, $C_{(5)}$–CH_3), δ 2.12 (br. s, $C_{(11)}$–CH_3), δ 2.65 (dd, J=2 and 12 Hz; $C_{(4\alpha)}$–H), δ 2.96 (m, $C_{(10\beta)}$–H), δ 5.28 (q, $J_{6\beta,13}$=1.5 Hz; $C_{(6\beta)}$–H), and δ 5.65 (d, $J_{9,10\beta}$=3 Hz; $C_{(9)}$–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.). $[\alpha]_D$ +93° (c=0.91, $CHCl_3$), $C_{15}H_{18}O_4$[2] (M^+ at m/e 262); ν_{max}^{Nujol} 1786, 1739, and 1684 cm^{-1}; λ_{max}^{EtOH} 217 nm (ε 19300); PMR ($CDCl_3$): δ 1.29 (s, $C_{(5)}$–CH_3), δ 2.00 (t, $J_{6\beta,13}$=2 Hz; $J_{8\beta,13}$=2 Hz; $C_{(11)}$–CH_3), δ 4.75 (m, $C_{(8\beta)}$–H), δ 5.05 (br. s,

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[10] An alternative structure with 8α-OH configuration would show a different PMR spectrum from that of **5** (with 8β-H configuration).

[11] Y. Ishizaki, Y. Tanahashi, T. Takahashi, and K. Tori, *Chem. Comm.*, **1969**, 551.

[12] Oxidation of atractylon and linderene 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 ($C_{(8\beta)}$–H or $C_{(8\beta)}$–OH). PMDR experiments showed the presence of long-range spin-couplings of the olefinic $C_{(11)}$–CH_3 protons to the $C_{(6\beta)}$–H (at δ 5.18 for **2** and at δ 5.05 for **3**) and to the $C_{(8\beta)}$–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.

$\mathrm{C}_{(6\beta)}$–H)]. Reduction of **2** with sodium borohydride in methanol yielded **3**. The structure of **3** must be shown as eremophil-7(11)-ene-12,8α; 14β,6α-diolide (**3**),[14] since **1** was reduced with sodium borohydride to form **5** with a loss of the hydroxyl group at $\mathrm{C}_{(8\beta)}$. The spectral data described above are compatible with the structure (**3**).

Finally, 6β-hydroxyeremophil-7(11)-en-12,8α-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.

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Opening of the Cephalosporin Dihydrothiazine Ring

2-Ethoxy-3-cephem-1β-oxide (**3**) was found to be thermally unstable and easily converted into isothiazolones (**4**, **5**, **6**, **9**, **10**), and the β-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-methylthio- or 2-methoxycephalosporins into azlactone derivatives similar to the penicillin-penicillenate rearrangement reaction.[2] This reaction suggested that introduction of a heteroatom substituent at C(2) of cephem molecules would facilitate ring opening of the dihydrothiazine moiety. Further, we wish to add herein other transformation reactions of 2-alkoxycephems involving S(1)–C(2) bond fission.

Treatment of methyl 7β-benzamido-3-methyl-3-cephem-4-carboxylate[3] (**1**) with 1.2 equivalents of *tert*-butyl hypochlorite in ethanol-containing methylene chloride (0°, 1 day, 45% yield) gave a 2α-ethoxy-3-cephem (**2**, mp 178—179.5°[4]).[5] Successive oxidation of **2** with 1 equivalent of *meta*-chloroperbenzoic acid in chloroform (0°, 1 hr, 73% yield) afforded a 2α-ethoxy-1β-oxide [**3**, mp 137—138°; IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3320, 1785, 1736, 1660, 1543; NMR ($\mathrm{CDCl_3}$) δ ppm: 1.20 (3H, t, $J=7$, $-\mathrm{OCH_2C\underline{H}_3}$), 2.12 (3H, s, 3-$\mathrm{CH_3}$), 3.80 (3H, s, $-\mathrm{COOCH_3}$), 4.60 (1H, d, $J=5.5$, H-6), 4.63 (1H, s, H-2), 6.25 (1H, dd, $J=5.5$ and 10, H-7)]. The 2α-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°; IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3430, 1734, 1660, 1524;

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1) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), 23, 2518 (1975).
2) H. Bundgaard, *J. Pharm. Sci.*, **60**, 1273 (1971) and the related references cited therein.
3) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), 23, 2507 (1975).
4) All compounds were characterized by infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry and also by elementary analysis.
5) *cf.* D.O. Spry, *Tetrahedron Letters*, **1972**, 3717.