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Photochemical Oxidation. II.[1] Biogenetic-Type Conversion of Ligularol and Furanoeremophilane into 6β-Hydroxyeremophilenolide and Eremophilenolide

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Ligularol and furanoeremophilane were converted into 6β-hydroxyeremophilenolide and eremophilenolide *via* photochemical oxidation

Keywords——ligularol; 6β-hydroxyeremophilenolide; furanoeremophilane; eremophilenolide; ligularone; photochemical oxidation

It has been shown that furanosesquiterpenes of eremophilane type (Ia and Ib) coexist in nature with their analogues (IIa and IIb) in which furan ring of Ia and Ib are replaced by α,β-unsaturated butenolide.[3] Novotny and his co-workers[4] suggested that furanoeremophilane (Ia) served as a precursor of eremophilenolide (IIa) and also reported that 8, 12-dimethoxy-8,12-dihydrofuranoeremophilane (IIIa) coexisted with Ia and Ib in a plant. Since it would be appropriate to expect the existence of biological sequence I→III→II, we have attempted to provide chemical analogy[5] for the above assumption. This paper deals with the conversion of ligularol (Ib) and Ia into 6β-hydroxyeremophilenolide (IIb) and IIa *via* photochemical oxidation.[6]

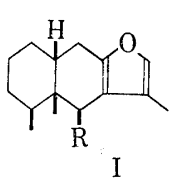
Ligularol acetate (Ic)[7] was photooxidized in methanol according to Schenck's method[8] to give 12-hydroperoxy-8-methoxy-8,12-dihydroligularol acetate (IIIb) and 6β-acetoxy-8-methoxyeremophilenolide (IV) in 33% and 60% yield, respectively. The structure of IIIb was confirmed by the following chemical and spectral data. IIIb liberated iodine from potassium iodide-acetic acid solution, in accord with the presence of O–O bond. The infrared (IR) spectrum shows absorption bands at 3420 (OOH) and 1725 cm^{-1} (CH_3CO_2). The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) shows signals at 0.80 (3H, d, J=4, C_4–CH_3), 0.98 (3H, s, C_5–CH_3), 1.95 (3H, s, C_{11}–CH_3), 2.05 (3H, s, CH_3CO_2), 3.10 (3H, s, OCH_3), 5.80 (1H, s, C_6–H), 5.62 (1H, s, C_{12}–H) and 9.49 (1H, s, OOH). The structure of IV was also supported by the following spectral data. The IR spectrum shows absorption bands at 1755, 1750 and 1685 cm^{-1} due to an α,β-unsaturated butenolide and ester group. The NMR spectrum ($CDCl_3$) shows signals at 0.86 (3H, d, J=4, C_4–CH_3), 1.03 (3H, s, C_5–CH_3), 2.00 (3H, s, C_{11}–

1) Part of this work was presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April, 1969; Part I: Z. Horii, K. Ohkawa, and C. Iwata, *Chem. Pharm. Bull.* (Tokyo), **20**, 624 (1972).
2) Location: *133-1, Yamadakami, Suita, Osaka.*
3) *a*) H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc.* (*C*), **1966**, 1545; *b*) J. Hochmannova, L. Novotny, and V. Herout, *Collection Czech. Chem. Commun.*, **27**, 1872 (1962); *c*) L. Novotny and V. Herout, *ibid.*, **30**, 3579 (1965).
4) L. Novotny, Z. Samek, and F. Sorm, *Collection Czech. Chem. Commun.*, **31**, 371 (1966).
5) one step conversion of I into II was reported by two groups: Ishii and his co-workers.[3a]: Ib→IIb, oxidation with monoperphthalic acid (*ca.* 9% yield); L. Novotny, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **29**, 2189 (1964): Ia→IIa, oxidation with oxygen (*ca.* 10% yield).
6) While preparing this manuscript, the photochemical oxidation of Ia has been reported by the following workers: K. Naya, R. Kanazawa, and M. Sawada, *Bull. Chem. Soc. Jpn*, **48**, 3220 (1975).
7) H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, **21**, 2605 (1965).
8) C.S. Foote, M.T. Wuesthoff, S. Wexler, I.G. Burstain, R. Denny, G.O. Schenck, and K-H. Schulte-Elte, *Tetrahedron*, **23**, 2483 (1967).

CH_3), 2.11 (3H, s, CH_3CO_2), 3.08 (3H, s, OCH_3) and 5.70 (1H, s, C_6-H). Chromatography of IIIb on basic alumina with ether gave the lactone (IV) in 61% yield.

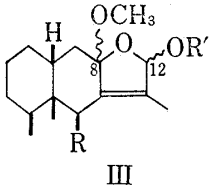
Hydrolysis of the lactone (IV) with sodium hydroxide gave 6β,8-dihydroxyeremophilenolide (V) in 53% yield. Reduction of V with sodium borohydride gave IIb in 94% yield, which was identical with the natural 6β-hydroxyeremophilenolide. Hydrogenation of IIIb in acetic acid over platinum oxide gave IIc, which was hydrolyzed with diluted hydrochloric acid to give IIb in 17% yield (from IIIb).

Photooxidation of Ia prepared by reduction of ligularone[7] with lithium aluminum hydride-aluminum chloride gave a mixture of the hydroperoxy and lactone derivative which was hydrolyzed with diluted sodium hydroxide to give 8-hydroxyeremophilenolide (VI) in 29% yield. Reduction of VI with sodium borohydride in methanol gave IIa in 90% yield, which was identical with the natural eremophilenolide.



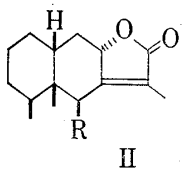
I

Ia : R=H
Ib : R=OH
Ic : R=OAc



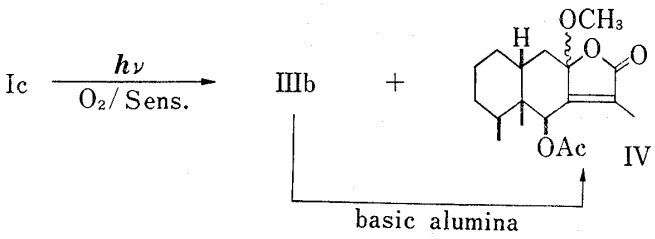
III

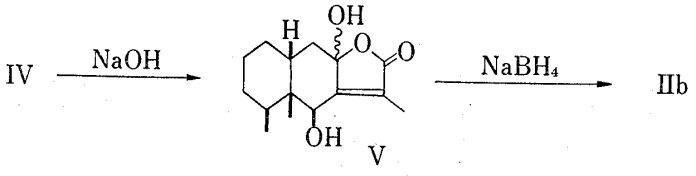
IIIa : R=H, R′=CH_3
IIIb : R=OAc, R′=OH
IIIc : R=OAc, R′=H

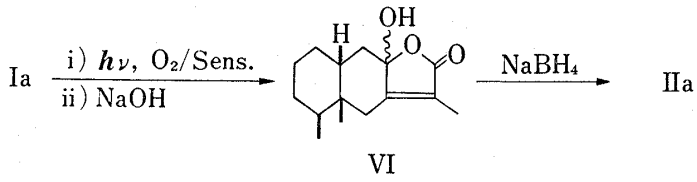


II

IIa : R=H
IIb : R=OH
IIc : R=OAc







Experimental[9]

Photooxidation of Ligularol Acetate (Ic)——A solution of Ic (200 mg) and Rose Bengal (10 mg) in MeOH (250 ml) through which oxygen was bubbled, was irradiated with a 100 W high pressure mercury lamp at 10—20° for 20 min. The reaction mixture was evaporated at 40—50° with a rotary evaporator. Then petr. ether was added to the residue, and the separated precipitate was recrystallized from ether to give

9) All melting points are uncorrected. The following instruments were used for the physical data. NMR spectra: Hitachi Perkin-Elmer H-60; IR spectra: Hitachi IR Spectrometer EPI-G 3; ORD: JASCO Model ORD/UV/CD-5; Mass spectra (MS); Hitachi Mass Spectrometer Model RMU-6; Optical rotation value: Yanagimoto OR-20 Model. Eikosha PIH-100 from Eikosha Co., Osaka, was used as light sourse for the photoreaction. Organic extracts were dried over anhydrous Na_2SO_4.

IIIb (82 mg, 33%), mp 151—152°. *Anal.* Calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.52; H, 8.23. Chromatography of IIIb on alumina (Woelm, basic) with ether as eluent gave IV in 61% yield.

The above petr. ether solution was evaporated under reduced pressure and the residue was chromatographed on alumina (Merck, activity II—III) with ether as eluent. The first eluate gave crystals which were recrystallized from petr. ether to give IV (114 mg, 49%), mp 177—178°. *Anal.* Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.51; H, 8.09.

6β,8-Dihydroxyeremophilenolide (V)——A mixture of IV (130 mg), 10% NaOH (0.5 ml), MeOH (20 ml), and H_2O (40 ml) was stirred at room temperature for 5 hr. The reaction mixture was acidified with 5% HCl and extracted with ether. The ether extract was washed with satd. $NaHCO_3$ and H_2O, dried, and evaporated. Preparative thin-layer chromatography (TLC) of the residue on silica gel (Mallinckrodt PF_{254}) with $CHCl_3$–MeOH (10: 1) as developing solvent gave V (57 mg, 53%), mp 210—211° (from ether). IR ν_{max}^{KBr} cm^{-1}: 3510 (OH), 3250 (OH), 1740 (lactone), and 1708 (C=C). MS *m/e*: 266 (M^+). *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 67.64; H, 8.33. Found: C, 67.79; H, 8.12. NMR (d_6-DMSO) δ: 0.69 (3H, broad d, C_4–CH_3), 1.00 (3H, s, C_5–CH_3), 1.75 (3H, s, C_{11}–CH_3), 4.88 (1H, d, J=6, C_6–OH), and 7.10 (1H, s, C_8–OH).

6β-Hydroxyeremophilenolide (IIb)——From IIIb: A solution of IIIb (41 mg) in AcOH (4 ml) was hydrogenated over PtO_2 (20 mg) at room temperature under atmospheric pressure. After the uptake of 1.3 molar equivalent of hydrogen (30 min.), the catalyst was removed by filtration and sated. $NaHCO_3$ was added to the filtrate. The alkaline mixture was extracted with ether. The ether extract was washed with H_2O, dried, and evaporated. Chromatography of the residue on alumina (Merck, activity II—III) with ether as eluent gave IIc (10 mg, 29%) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (lactone) and 1740 (ester)], which was mixed with 10% HCl (3 ml) and then heated on a water bath for 1 hr. After cooling, the reaction mixture was extracted with ether. The ether extract was washed with satd. $NaHCO_3$ and H_2O, dried, and evaporated. Recrystallization of the residue from ether gave IIb (5 mg, over all 17%), mp 208°, $[\alpha]_D^{25}$ −260° (c=0.5, MeOH). This product (IIb) was identified by comparison with the natural 6β-hydroxyeremophilenolide.

From V: To a stirred solution of V (53 mg) in MeOH (20 ml) was added $NaBH_4$ (100 mg) under ice-H_2O cooling. The reaction mixture was stirred for 2 hr at room temperature and then concentrated to one half volume under reduced pressure. The residual solution was acidified with 5% HCl and extracted with ether. The ether extract was washed with satd. $NaHCO_3$ and H_2O, dried, and evaporated. Recyrstallization of the residue from ether gave IIb (48 mg, 94%), mp 208°.

Franoeremophilane (Ia)——To a solution of $AlCl_3$ (700 mg) in anhyd. ether (5 ml) was added $LiAlH_4$ (100 mg), and to this stirred suspension was added dropwise a solution of ligularone (250 mg) in anhyd. ether (10 ml). The reaction mixture was stirred at room temperature for 20 min and then refluxed for 20 min. Excess of $LiAlH_4$ was decomposed by adding of AcOEt. To the resulting mixture was added H_2O and ice, and the ether layer was separated. The H_2O layer was extracted with ether. The ether extract was combined with the above ether layer and washed with satd. $NaHCO_3$ and H_2O, dried, and evaporated. Distillation of the residue gave Ia (190 mg, 80%), bp 85° (1 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 and 1565 (furan ring). MS *m/e*; 218 (M^+). This product was identified by comparison with the natural furanoeremophilane.

8-Hydroxyeremophilenolide (VI)——A solution of Ia (190 mg) and Rose Bengal (10 mg) in a mixture of CH_2Cl_2 (20 ml) and MeOH (230 ml) was photooxidized under similar conditions as the above described Ic. The reaction mixture was evaporated at 40—50° with a rotary evaporator. Chromatography of the residue on alumina (Merck, activity II—III) with ether as eluent gave an oily mixture of the lactone and hydroperoxy derivatives (162 mg). A mixture of the above oil, 1% NaOH (40 ml) and MeOH (20 ml) was stirred at room temperature for 7 hr. The reaction mixture was acidified with 5% HCl and extracted with ether. The ether extract was washed with satd. $NaHCO_3$ and H_2O, dried, and evaporated. Preparative TLC of the residue on silica gel (Mallinckrodt, PF_{254}) with $CHCl_3$–MeOH (20: 1) as developing solvent gave VI (74 mg, 26%), mp 214° (from benzene–*n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 3290 (OH) and 1730 (lactone). MS *m/e*: 250 (M^+). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.13; H, 8.84.

Eremophilenolide (IIa)——To a stirred solution of VI (46 mg) in MeOH (10 ml) was added $NaBH_4$ (80 mg) under ice-H_2O cooling. The reaction mixture was stirred for 3 hr at room temperature and acidified with 5% HCl, and extracted with ether. The ether extract was washed with satd. $NaHCO_3$ and H_2O, dried, and evaporated. Recrystallization of the residue from ether gave IIa (39 mg, 90%), mp 124—126°. IR ν_{max}^{KBr} cm^{-1}: 1724 (lactone). MS *m/e*: 234 (M^+). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.74; H, 9.72. This product (IIa) was identified by comparison with the natural eremophilenolide.

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