The Photosensitized Oxygenation of Furanoeremophilanes. I. The Isomeric Hydroperoxides from Petasalbin and Their Transformations to Lactones

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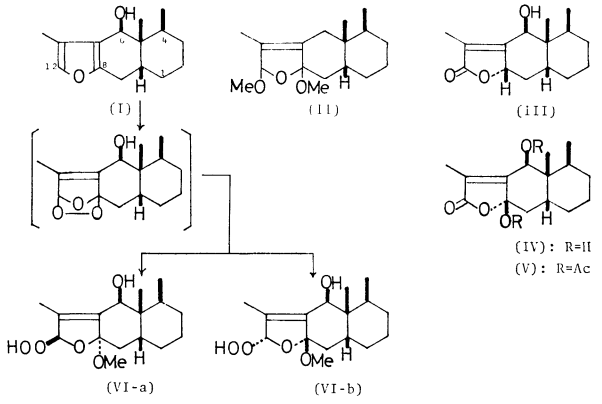
The photosensitized oxygenation of petasalbin I gave almost quantitatively a crystalline mixture of two isomeric hydroperoxides, V-a and V-b, both of which were then transformed to the corresponding lactones, VI-a and VI-b, respectively, in good yields. The stereochemistry of these hydroperoxides and lactones has been established by spectral and chemical methods. Furthermore, two natural lactones, III and IV, were prepared by the reduction of the hydroperoxides.

Petasalbin I has been isolated from *Petasites*[1] and *Ligularia*[2,3] species, and its absolute configuration has already been established. Then, from *Petasites officinalis* an interesting compound, II, was isolated by Šorm *et al.*, and for its formation it was postulated that the peroxides of methanol must play a role in a plant.[4,5] On the other hand, the dye-sensitized photooxygenation of furans has been extensively studied[6,7] and the oxygenation mode in methanol has been demonstrated, in that the reaction proceeds to give a cyclic peroxide by the 1,4-addition of oxygen to a furan ring, an addition which is often followed spontaneously by the addition of methanol, thus affording a 2-methoxy-2,5-dihydrofuran derivative.[6]

We have oureselves previously investigated the photosesnsitized oxygenation[8] of petasalbin I isolated from *Petasites japonicus* Maxim. as a biogenetic-type oxidation to the lactone homologues, such as the known 6β-hydroxyeremophilenolide, III,[2] and the newly isolated 6β,8β-dihydroxyeremophilenolide, IV, included in the same plant.

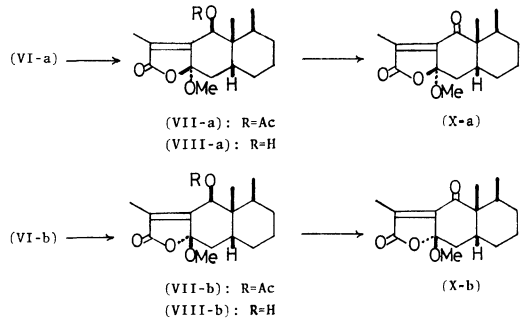
The present paper will report on the physical and chemical properties of the hydroperoxides, VI-a and VI-b, prepared from petasalbin I, and also on the stereochemistry of the hydroperoxides, VI-a,b, and their derivatives. Furthermore, the reduction products of VI-a,b were examined and found to include the same products as the natural lactones, III and IV.



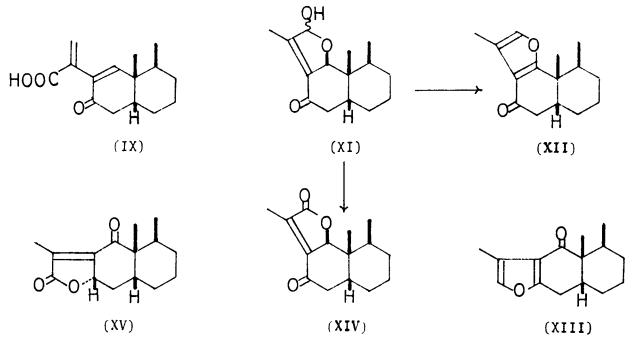
Scheme 1

Petasalbin I in methanol was photooxygenated, in the presence of Rose Bengal as a sensitizer, by irradiation with a circular fluorescent lamp (30 watt) under a bubbling of air. The reaction mixture was found on tlc to contain two compounds, which were separated by careful fractional crystallization to afford two hydroperoxides, (VI-a) (mp 119.3—119.5 °C (dec)) and (VI-b) (mp 116.0—116.5 °C (dec)). Both compounds have the same molecular formula, $C_{16}H_{26}O_5$, and both are positive to a peroxide test (KI–AcOH). Thus, there was no symptom of the exsistence of a cyclic ozonide-like intermediate, as in Scheme 1, and we could initially obtain the methanol adducts, VI-a,b, whose IR, UV, and NMR spectra were very similar to each other, suggesting that both are stereoisomers caused by a newly introduced 2-methoxy-5-hydroperoxy-2,5-dihydrofuran grouping. They showed these UV spectra: end absorption in both; IR bands at 3480 and 3350 (H-bonded OH), 1700 and 1630 cm^{-1} (C=C double bond) in VI-a, and at 3400 and 3330 (H-bonded OH), 1700 and 1630 cm^{-1} (C=C double bond) in VI-b; NMR signals (acetone-d_6): δ 11.13 (s, OO–H), 5.58 (s, OOCH), 3.08 (s, OCH_3) in VI-a, and 11.25 (s, OO–H), 5.70 (s, OOCH), 3.15 (s, OCH_3) in VI-b, besides the common signals with the original petasalbin I. The above results, therefore, led to the VI-a and VI-b structures for the hydroperoxides except for the configuration of the 8-methoxy and 12-hydroperoxy groups. These hydroperoxides, VI-a,b, were relatively stable in the crystalline state, but decomposed considerably in solution or upon chromatography on silica gel (Merck, grade II). Furethermore, the reduction of the hydroperoxides, VI-a,b, with sodium sulfite, sodium borohydride, and a platinum catalyst gave no principal or selective reduction product and rather complicated results, accompanied by decomposition, as will be described in detail later.

Finally, the hydroperoxides, VI-a,b, were quantita-



Scheme 2



Scheme 3

tively converted to two substances, epimeric 6β-acetoxy-8α-methoxylactone (VII-a) (mp 106.5—108.0 °C) and the corresponding 8β-methoxylactone (VII-b) (mp 174.5—175.5 °C) by acetylation with acetic anhydride–pyridine.

For the determination of the configuration, therefore, each hydroperoxide was transformed into a 6-oxo derivative, X-a,b, according to Scheme 1—that is, by acetylation followed by the partial hydrolysis of the 6β-acetoxy group and subsequently by oxidation with Jones' reagent. Both the first products, VII-a and VII-b, showed similar IR bands at 1760 (α,β-unsaturated lactone C=O), and 1740 cm^{-1} (C=C double bond) and similar NMR spectra (cf. Table 1 and Experimental section). By subsequent partial hydrolysis, compounds VII-a and VII-b gave 6β-hydroxy derivatives, (VIII-a) (mp 167.5—168.0 °C) and (VIII-b) (mp 129.5—130.2 °C), respectively, both of which showed NMR spectra closely similar to that of 6β-hydroxyeremophilenolide III except for the signals due to the 8-methoxy groups instead of the 8β-proton in III. On the other hand, a mixture of the 6β-acetoxy-8(α and β)-methoxylactones, VII-a,b, was treated with an excess of alkaline to afford quantitatively an acid (IX) as the sole product. The IX acid, $C_{15}H_{20}O_3$ (mp 96.0—97.0 °C), exhibited IR bands at 3400—2400 (OH in carboxyl group), 1695 (C=O in carboxyl group), 1680 (α,β-unsaturated ketone), 1615 (C=C double bond), 950 cm^{-1} (end-methylene in a conjugated diene system); NMR signals at δ 6.70 (s, 1H, 6-H), 6.28 and 5.69 (each d, J=1.5 Hz, 13-CH_2=), and its UV maximum at 239 nm. The above results led to the IX structure for the acid; hence, the 6β-acetoxy compounds, VII-a and VII-b, obviously became epimers with regard to the configuration of the 8-methoxy groups.

The configurational assignments of the 8-methoxy groups in the corresponding epimers (VI—VIII, and IX) were achieved by a comparison of the NMR spectra, ORD-CD curves, specific rotations, and adsorption properties (Table 1, Fig. 1, and Fig. 2).

The conformation of α,β-unsaturated keto-group in a pair of 6-oxolactones, (X-a) (mp 99.0—100.0 °C) and (X-b) (mp 160.5—161.5 °C), was defined by the ORD-CD curves. Similar effects[9] observed in the cisoid α,β-unsaturated ketones are to be expected for the 6-oxo compounds, X-a,b. The X-a,b epimers have opposite signs; those enantiomeric chiralities seemed to be dominated by the helicity of the α,β-unsaturated ketone moiety. Thus, on the basis of a consideration with the Dreiding model, a pair of 6-oxolactones, X-a,b, with intense negative and positive Cotton effects in the 250—

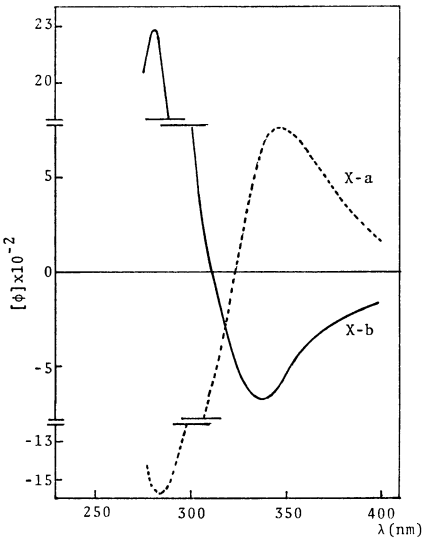


Fig. 1. Optical rotatory dispersion curves of 6-oxo-8-methoxylactones X-a and X-b.

Table 1. Comparison of chemical shifts (δ-values), specific rotations, and R_f values of the corresponding isomers

Compound	Solvent	15-Me	14-Me	13-Me	6-H	$[\alpha]_D^\circ$ ($CHCl_3$)	R_f (C_6H_6:AcOEt)
VI-a	CD_3COCD_3	0.78s	0.94d J=7.2	1.73d J=1.0	4.72b*	+2.5[a]	0.50 (3: 1)
VI-b	CD_3COCD_3	1.00s	0.72d J=5.5	1.73s	4.36s	+46.1[a]	0.40 (3: 1)
VII-a	$CDCl_3$	0.85s	0.97d J=7.6	1.85d J=1.4	5.92d J=1.4	−190.4	0.75 (10: 1)
VII-b	$CDCl_3$	0.98s	0.77d J=5.5	1.94s	5.62s	+185.5	0.66 (10: 1)
VIII-a	$CDCl_3$	0.78s	0.98d J=7.0	2.02d J=1.5	4.95d J=1.5	−187.0	0.73 (3: 1)
VIII-b	$CDCl_3$	1.08s	0.75d J=5.0	1.87s	4.49s	+205.1	0.66 (3: 1)
X-a	$CDCl_3$	1.04s	0.90d J=7.7	1.98s		−13.6	0.60 (30: 1)
X-b	$CDCl_3$	1.15s	0.66d J=6.0	1.96s		−16.6	0.60 (30: 1)

b*: broad singlet. a): measured with a methanol solution.

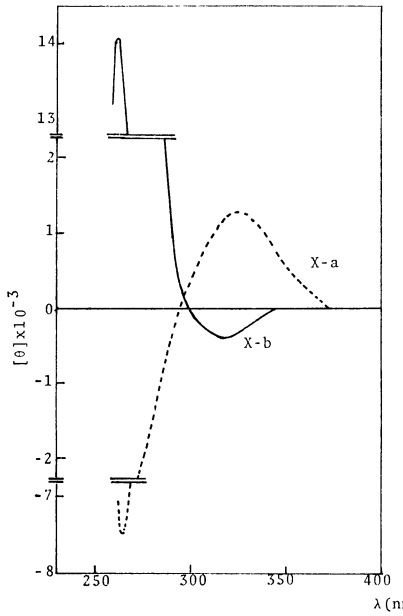


Fig. 2. Circular dichroism curves of 6-oxo-8-methoxy-lactone X-a and X-b.

400 nm region have been alloted the X-a and X-b formulas, those which have left- and right-handed helicities respectively.

In the NMR spectra, only the 8α-methoxy derivatives showed homoallylic couplings[10] (1.0—1.5 Hz) between 6–H and 13–CH_3. Upon the Dreiding model, the angles between the two bonds lie around 90° and 20° in the 8α- and 8β-methoxy derivatives respectively. The observed coupling, therefore, is consistent with the above assignment.

A further comparison between the corresponding 8-methoxy epimers also revealed the characteristics of this configurational correlation. The NMR spectra of the 8α-methoxy compounds exhibited chemical shifts due to 14-methyls at a lower field than those due to 15-methyls, and the chemical shifts were reversed in the 8β-epimers. The 8β-methoxy compounds have stronger positive rotations than the 8α-series except for the 6-oxo derivatives. The 8β-methoxy derivatives showed stronger adsorptive properties than the 8α-epimers, suggesting that the 8β- and 8α-series have *cis*- and *trans*-like geometries respectively, in agreement with the above configurational assignment.

Now the configuration of the hydroperoxides, VI-a and VI-b, can be explained in terms of the approved mechanism that the *cis*-1,4-addition of an oxygen molecule should occur from one side to the furan ring surface, followed by the attack of methoxide from another side to give hydroperoxides as in the stereoformulas, VI-a and VI-b.

Next we examined several reduction methods for the stabilization of the labile hydroperoxy group.

a) By Sodium Sulfite. After the photooxygenation of petasalbin I in methanol, the solution was immediately subjected to reduction with sodium sulfite without any isolation of hydroperoxides. The products were separated by repeated column chromatography on silica gel to afford 6β-hydroxyeremophilenolide (III, 7%) (mp 204.0—205.0 °C), 6β-hydroxy-8α-methoxyepieremophilenolide VIII-a (5%), and two other unknown products, (IV, 1.8%) and (XI, 36%).

The IV product, $C_{15}H_{22}O_4$ (mp 209.0—211.5 °C, $[\alpha]_D$ +172°), showed the presence of hydroxyl groups at 3500 and 3250 cm^{-1}, α,β-unsaturated γ-lactone groups at 1730 and 1695 cm^{-1}, and its UV maximum at 218 nm. The MS spectrum indicated the presence of two hydroxyl groups, *i. e.*, *m/e* 266 (M^+), *m/e* 248 (M−18), and *m/e* 230 (M−36). The structure was proved by a comparison of the NMR spectrum with those of 6β-hydroxyeremophilenolide III and the epimeric 6β-hydroxy-8-methoxylactones, VIII-a,b. The configuration of the 8-hydroxyl group was identified as β-substituent from the chemical shifts of the 14- and 15-methyls, and also from the absence of homoallylic coupling between 6–H and 13–CH_3, according to the generality mentioned above.

On the other hand, the crude extract from the rhizomes of *Petasites japonicus* Maxim. was reinvestigated in order to examine the lactone components by chromatography on silica gel; the natural 6β,8β-dihydroxyeremophilenolide (IV) (mp 211.0—212.0 °C, $[\alpha]_D$ +169°) was isolated from the polar part.

The XI product was a colorless oil and was positive to an Ehrlich test. XI showed IR bands at 3400 (OH), 1685, and 1650 cm^{-1} and its UV maximum at 250 nm (α,β-unsaturated ketone). The appearance of the above keto-group can be derived from the fission of the dihydrofuran ring, followed by the isomerization of the double bond and recyclization with the 6β-hydroxyl group. As the above color-test suggested that XI is closely connected with a furan derivative, XI was heated in acetic anhydride at 90 °C for 1 hr to afford quantitatively isoligularone (XII)[11] (mp 147.0—148.0 °C, $[\alpha]_D$ +39.0°), which was an isomer of ligularone (XIII)[1-b,c] (mp 66.0—67.5 °C), prepared from petasalbin I with chromium trioxide-pyridine. Jones' oxidation of XI gave 8-oxoisoeremophilenolide (XIV) (mp 76.5—77.5 °C, $[\alpha]_D$ +31.5°), which showed IR bands at 1760 (lactone C=O), 1695, and 1660 cm^{-1} and its UV maximum at 245 nm (α,β-unsaturated ketone). Its NMR spectrum showed signals at 5.42 (q, J=2.5 Hz, 6–H) and 1.92 (d, J=2.5 Hz, 13–CH_3) with homoallylic coupling. The XIV lactone distinctly differs from the isomeric keto-lactone (XV)[1-a] (mp 124.0—126.0 °C, $[\alpha]_D$ −27.1°), prepared from 6β-hydroxyeremophilenolide III by Jones' oxidation. The configuration, therefore, can be assigned the XIV formula.

The former alcohol, XI, was indicated to be an epimeric mixture attributable to the orientation of the 12-hydroxyl group in its NMR spectrum—namely, pairs of signals centered at 5.32 and 5.12 (1H), 5.69 and 5.55 (1H), and 0.78 and 0.70 due to the 6–H, 12–H, and 15–CH_3 groups respectively. However, attempts to separate the mixture were unsuccessful.

b) By Sodium Borohydride. A crystalline mixture of hydroperoxides, VI-a,b, was treated with a methanol solution of sodium borohydride at room temperature, and the product was chromatographed on deactivated alumina (Merck, grade IV) to afford petasalbin I (30.2 %) and 6β-hydroxyeremophilenolide III (20%).

c) By a Platinum Catalyst. On hydrogenation with a platinum catalyst in acetic acid, the hydroperoxides,

VI-a,b, gave III (3.7%), 6β-hydroxy-8α-methoxyepieremophilenolide VIII-a (18.4%), and 6β,8β-dihydroxyeremophilenolide IV (24.5%).

When a mixture of the VI-a,b hydroperoxides was chromatographed on silica gel (Merck, grade II) in order to separate them, the eluate included recovered hydroperoxides (52%), IV (21%), and a mixture of lactones VIII-a,b (9%).

These reductions and silica gel chromatography invariably showed poor reproducibilities in the yield ratios of their products.

Experimental

The IR, UV, ORD-CD, and mass spectra were taken with Hitachi EPI-G3, Cary 14, JASCO ORD-5, and Hitachi RMU-6 spectrophotometers respectively. The NMR spectra were recorded with a Hitachi R-20B (60 MHz) spectrometer, and the chemical shifts are reported in δ-values (with TMS as the internal reference). The optical rotations were measured with a Perkin-Elmer 141 polarimeter. The tlc were run on Kieselgel G (Merck).

Isolation of Petasalbin (I), 6β-Hydroxyeremophilenolide (III), and 6β,8β-Dihydroxyeremophilenolide (IV). The dried rhizomes of *Petasites japonicus* Maxim. were extracted with ether at room temperature. The neutral oil (24 g) was chromatographed on neutral alumina (400 g, grade III). Elution with benzene and then benzene–ethyl acetate (20: 1) gave two fractions, including mainly petasalbin I and 6β-hydroxyeremophilenolide III respectively. Each fraction was purified by repeated chromatography on alumina or silica gel and by subsequent recrystallization to afford petasalbin I (2 g, tlc: R_f, 0.30, benzene) and 6β-hydroxyeremophilenolide III (1.9 g, tlc: R_f, 0.50, benzene–ethyl acetate, 5: 1).

The collected polar fraction (40 g), eluted with benzene–ethyl acetate (20: 1), was chromatographed on silica gel (400 g) with the same solvent to give crude III (1.4 g) and 6β,8β-dihydroxyeremophilenolide IV (2.2 g, R_f, 0.53, benzene–ethyl acetate, 2: 1).

Petasalbin (I):[1c] mp 79.0—81.0 °C, colorless needles (from ether or light petroleum), $[\alpha]_D^{22}$ −13.0° (*c*, 1.0, $CHCl_3$). (Found: C, 76.64; H, 9.40%).

6β-Hydroxyeremophilenolide (III):[2] mp 204.5—205.5 °C, colorless prisms (from ethyl acetate), $[\alpha]_D^{23}$ +203° (*c*, 1.01, $CHCl_3$). (Found: C, 72.05; H, 8.80%). The spectral data of the above compounds, I and III, are consistent with those reported in the lit. for 1-c and 2).

6β,8β-Dihydroxyeremophilenolide (IV): mp 211.0—212.0 °C, prisms (from methanol or ethyl acetate); $[\alpha]_D^{16}$ +169° (*c*, 0.985, $CHCl_3$); IR ($CHCl_3$): 3525, 3250, 1760, 1005, 990 cm^{-1}; NMR ($CDCl_3$): 4.60 (s, 6-H), 2.70 (br s, 2×OH), 2.07 (s, 9-CH_2), 1.87 (s, 13-CH_3), 1.11 (s, 15-CH_3), 0.78 (non-resolvable methyl signal, 14-CH_3).

Found: C, 67.46; H, 8.42%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

6β,8β-Diacetoxyeremophilenolide (V). 6β,8β-Dihydroxyeremophilenolide IV (241 mg) was dissolved in acetic anhydride (2.5 ml) and pyridine (1 ml), and the mixture was left at room temperature for 3 days. Subsequent working up in the usual manner gave quantitatively a crude diacetate, which was crystallized from isopropyl ether as prisms; mp 119.5—120.5 °C; $[\alpha]_D^{23}$ +64.7° (*c*, 1.00, $CHCl_3$); IR(KBr): 1780, 1760, 1740, 1250, 1170, 993 cm^{-1}, ($CHCl_3$): 1765, 1740sh, 1240, 993 cm^{-1}; NMR (CCl_4): 5.78 (s, 6-H), 1.95 (s, 13-CH_3), 1.90 (s, 2×OAc), 0.95 (s, 15-CH_3), 0.83 (non-resolvable methyl signal, 14-CH_3).

Found: C, 64.89; H, 7.36%. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48%.

The Photosensitized Oxygenation of Petasalbin (I) and Isolation of Hydroperoxides, (VI-a) and (VI-b). A stirred solution of petasalbin I (1.19 g) and Rose Bengal (47.5 mg) in methanol (60 ml) was irradiated with a circular fluorescent lamp (30 watt) for 3 hr under the bubbling of air. After the subsequent evaporation of the methanol *in vacuo*, the residue was extracted with benzene. The benzene extract was washed with water, and passed through a column filled with anhydrous sodium sulfate for drying and taking out the dye-stuff. On tlc, the benzene solution showed the existence of two products. The removal of the solvent *in vacuo* gave a colorless, crystalline mixture (1.4 g) of hydroperoxides, VI-a (R_f, 0.50, benzene–ethyl acetate, 3: 1) and VI-b (R_f, 0.40). The mixture was separated by fractional recrystallization from benzene. Thus, the evaporation of the solvent to some extent deposited a less-soluble compounds, VI-a; subsequently the mother liquor was fractionated by crystallization to collect VI-a and then VI-b.

Hydroperoxide (VI-a): mp 119.3—119.5 °C, colorless needles (from benzene), $[\alpha]_D^{24}$ +2.5° (*c*, 1.02, MeOH); positive to a peroxide test (KI–AcOH); IR(KBr): 3480, 3350, 1700, 1630, 1140, 1060, 930 cm^{-1}; MS: *m/e* 280 (M^+-18), *m/e* 109 (base peak); NMR (acetone-d_6): 11.13 (s, OO-H), 5.58 (s, OO-CH), 4.72 (split br s, 6-H), 4.13 (s, 6-OH), 3.08 (s, OCH_3), 1.99 (s, 9-CH_2), 1.73 (d, J=1.0 Hz, 13-CH_3), 0.94 (d, J=7.2 Hz, 14-CH_3), 0.78 (s, 15-CH_3).

Found: C, 64.37; H, 8.74%. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78%.

Hydroperoxide (VI-b): mp 116.0—116.5 °C, $[\alpha]_D^{24}$ +46.1° (*c*, 1.01, MeOH); positive to a peroxide test; IR(KBr): 3400, 3330, 1700, 1630, 1135, 1075, 980 cm^{-1}; MS: *m/e* 262 (M^+-36), *m/e* 78 (base peak); NMR (acetone-d_6): 11.25 (s, OO-H), 5.70 (s, OO–CH), 4.36 (s, 6-H), 4.22 (s, 6-OH), 3.15 (s, OCH_3), 1.73 (s, 13-CH_3), 1.00 (s, 15-CH_3), 0.72 (d, J=5.5 Hz, 14-CH_3).

Found: C, 64.75; H, 9.02%. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78%.

6β-Acetoxy-8α-methoxyepieremophilenolide (VII-a). Hydroperoxide VI-a (171.4 mg) was dissolved in pyridine (0.5 ml) and acetic anhydride (1 ml), and the mixture was left overnight at room temperature. Subsequent working up in the usual manner gave quantitatively the VII-a acetate, which was then crystallized from isopropyl ether as prisms: mp 106.5—108.0 °C, $[\alpha]_D^{24}$ −190.4° (*c*, 1.01, $CHCl_3$); UV: λ_{max}^{MeOH} 217 nm (ε, 10500); IR(KBr): 1760, 1740, 1700, 1230, 1060, 960 cm^{-1}; NMR ($CDCl_3$): 5.92 (d, J=1.4 Hz, 6-H), 3.20 (s, 8-OCH_3), 2.16 (s, 6-OAc), 1.85 (d, J=1.4 Hz, 13-CH_3), 0.97 (d, J=7.6 Hz, 14-CH_3), 0.85 (s, 15-CH_3).

Found: C, 67.10; H, 8.15%. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13%.

6β-Acetoxy-8β-methoxyeremophilenolide (VII-b). Hydroperoxide VI-b (125.5 mg) was acetylated in a similar manner to afford the acetate (VII-b, 118.2 mg), which was then crystallized from isopropyl ether as prisms: mp 174.5—175.5 °C, $[\alpha]_D^{23}$ +185.5° (*c*, 1.03, $CHCl_3$); IR(KBr): 1760, 1740, 1700, 1250, 1180, 1080, 925 cm^{-1}; NMR ($CDCl_3$): 5.62 (s, 6-H), 3.00 (s, 8-OCH_3), 2.05 (s, 6-OAc), 1.94 (s, 13-CH_3), 0.98 (s, 15-CH_3), 0.77 (d, J=5.5 Hz, 14-CH_3).

Found: C, 67.25; H, 8.13%. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13%.

Alkaline Hydrolysis of Acetates, (VII-a) and (VII-b). a) 6β-Hydroxy-8α-methoxyepieremophilenolide (VIII-a). The acetate VII-a (65.7 mg) was dissolved in an equimolecular potassium hydroxide–methanol solution (0.93 ml, 0.22 N), after which the mixture was left at room temperature for 1 hr. After the removal of the solvent and acidification with 1% sulfuric

acid, the reaction mixture was extracted with ether. The extract was washed with a saturated sodium hydrogen carbonate solution and water. The subsequent evaporation of the solvent gave 6β-hydroxy-8α-methoxyepieremophilenolide VIII-a (50 mg), which was then crystallized from light petroleum as needles: mp 167.5—168.0 °C, $[\alpha]_D^{23}$ −187.0° (*c*, 0.96, $CHCl_3$); IR(KBr): 3460, 1740, 1680, 1165, 1080, 1070, 940 cm^{-1}; UV: λ_{max}^{MeOH} 225 nm (ε, 7500); MS: *m/e* 280 (M^+), *m/e* 109 (base peak); NMR ($CDCl_3$): 4.95 (d, J=1.5 Hz, 6-H), 3.14 (s, 8-OCH_3), 2.62 (s, OH), 2.02 (d, J=1.5 Hz, 13-CH_3), 0.98 (d, J=7.0 Hz, 14-CH_3), 0.78 (s, 15-CH_3).

Found: C, 68.60; H, 8.68%. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63%.

b) 6β-Hydroxy-8β-methoxyeremophilenolide (VIII-b). The hydrolysis of the acetate VII-b (222 mg) was performed in a similar manner. The product was obtained quantitatively and was crystallized from ethyl acetate–light petroleum as prisms: mp 129.5—130.2 °C, $[\alpha]_D^{23}$ +205.1° (*c*, 1.01, $CHCl_3$); IR(KBr): 3450, 1730, 1690, 1210, 1190, 1130, 1090, 920 cm^{-1}, ($CHCl_3$): 3500, 1755, 1010, 1002, 992, 970, 930 cm^{-1}; NMR ($CDCl_3$): 4.49 (s, 6-H), 3.27 (s, 8-OCH_3), 2.71 (s, 6-OH), 2.00 (s, 9-CH_2), 1.87 (s, 13-CH_3), 1.08 (s, 15-CH_3), 0.75 (d, J=5.0 Hz, 14-CH_3).

Found: C, 68.87; H, 8.71%. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63%.

Alkaline Hydrolysis of the Mixture of 6β-Acetoxy-8(α and β)-Methoxylactones, (VII-a) and (VII-b). A mixture of 6β-acetoxy-8(α and β)-methoxylactones, VII-a, b was prepared from petasalbin I by photooxidation as has been described above, followed by acetylation. The crystalline mixture (6.138 g) was dissolved in a 1.84 N potassium hydroxide–methanol solution (80 ml) and then left at room temperature for 36 hr. After acidification with 2 N sulfuric acid, the mixture was extracted with ether. Subsequent working up in the usual manner gave a viscous oil (5.41 g), which crystallized on standing. The crystalline mass was recrystallized from isopropyl ether-light petroleum to afford the pure unsaturated acid IX (4.07 g) as needles: mp 96.0—97.0 °C, $[\alpha]_D^{22}$ +20.5° (*c*, 1.09, $CHCl_3$); IR (CCl_4): 3400—2300, 1695, 1680, 1615, 950, 928 cm^{-1}; UV: λ_{max}^{MeOH} 239 nm (ε, 5580); MS: *m/e* 248 (M^+), 133 (base peak); NMR (CCl_4): 10.5 (br s, COOH), 6.70 (s, 6-H), 6.28 and 5.69 (each d, J=1.5 Hz, 13-CH_2=), 1.13 (s, 15-CH_3), 0.92 (d, J=6.7 Hz, 14-CH_3).

Found: C, 72.24; H, 7.88%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

Jones' Oxidation. a) 6-Oxo-8α-methoxyepieremophilenolide (X-a). Jones' reagent (0.18 ml) was added to a stirred solution of 6β-hydroxy-8α-methoxylactone VIII-a (97.8 mg) in acetone (4 ml) over a period of 0.5 hr under cooling with ice-water. After stirring for a further 2.5 hr and after the decomposition of the excess reagent with methanol, the mixture was extracted with ether. Subsequent working up as usual gave, quantitatively, 6-oxo-8α-methoxyepieremophilenolide, X-a (mp 99.0—100.0 °C), as needles (from isopropyl ether), $[\alpha]_D^{23}$ −13.6° (*c*, 1.04, $CHCl_3$); IR (KBr): 1760, 1698, 1660, 1160, 1070, 915 cm^{-1}; UV: λ_{max}^{MeOH} 230 nm (ε, 8300); NMR ($CDCl_3$): 3.16 (s, 8-OCH_3), 2.35 (m, 3H), 1.98 (s, 13-CH_3), 1.04 (s, 15-CH_3), 0.90 (d, J=7.7 Hz, 14-CH_3); ORD (*c*, 0.116, MeOH): *cf.* Fig. 1; CD (*c*, 0.108, MeOH): Fig. 2.

Found: C, 69.04; H, 8.14%. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

b) 6-Oxo-8β-methoxyeremophilenolide (X-b). Compound VIII-b (103.7 mg) was oxidized by a method similar to that described above to yield 6-oxo-8β-methoxyeremophilenolide, X-b (94.3 mg) (mp 160.5—161.5 °C), as prisms (from isopropyl ether); $[\alpha]_D^{23}$ −16.6° (*c*, 1.04, $CHCl_3$); negative to a Zimmermann test;[12] UV: λ_{max}^{MeOH} 230 nm (ε, 7630); IR (KBr): 1775, 1695, 1175, 995, 925 cm^{-1}, ($CHCl_3$): 1763, 1690, 1178, 998, 927 cm^{-1}; NMR ($CDCl_3$): 3.14 (s, 8-OCH_3), 2.26 (s, 3H), 1.96 (s, 13-CH_3), 1.15 (s, 15-CH_3), 0.66 (d, J=6.0 Hz, 14-CH_3); ORD (*c*, 0.118, MeOH): *cf.* Fig. 1; CD (*c*, 0.099, MeOH): Fig. 2.

Found: C, 69.02; H, 8.08%. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

Chromatography of Hydroperoxides on Silica Gel. A crystalline mixture of hydroperoxides, VI-a, b (1.109 g), was chromatographed on silica gel (26.5 g, grade II). Elution with benzene–ethyl acetate (50: 1 and 20: 1) gave a mixture of 6β-hydroxy-8(α and β)-methoxylactones VII-a, b (94 mg), the recovered starting hydroperoxides, VI-a, b (576 mg), and 6β,8β-dihydroxyeremophilenolide IV (209 mg). The compounds, VII-a, b and VI-a, b, were identified by tlc analysis.

Compound IV was crystallized from ethyl acetate as prisms; mp 209.0—211.5 °C, $[\alpha]_D^{24}$ +172° (*c*, 0.97, $CHCl_3$).

Found: C, 67.52; H, 8.32%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

The acetate was prepared in a similar manner and crystallized from isopropyl ether as prisms; mp 119.5—120.5 °C.

Found: C, 65.31; H, 7.58%. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48%. Compound IV and its acetate were identified with the natural samples by a mixed-melting-point determination and by a comparison of their IR, UV, and NMR spectra.

Reduction of Hydroperoxides (VI-a, b). a) By Sodium Sulfite. A mixture of petasalbin I (500 mg) and Rose Bengal (30 mg) in methanol (50 ml) was photooxygenated as has been described above. A solution of sodium sulfite (700 mg) in water (10 ml) was added to the stirred mixture, and stirring was continued for 15 hr. After the removal of the methanol and the addition of water, the mixture was extracted with ether. The extract was worked up in the usual manner to give a crude product (427 mg), which was then chromatographed on silica gel (15 g, grade II). Elution with benzene–ethyl acetate (30: 1) gave 6β-hydroxy-8α-methoxyepieremophilenolide VIII-a (30 mg), hemiacetal XI (193 mg), 6β-hydroxyeremophilenolide III (38 mg), and 6β,8β-dihydroxyeremophilenolide IV (10.5 mg).

The above compounds, III (mp 204.0—205.0 °C: prisms from ethyl acetate; $[\alpha]_D^{23}$ +212° (*c*, 1.02, $CHCl_3$), was found to be identical with the natural specimen by a mixed-melting-point determination and by a comparison of their IR and NMR spectra.

Hemiacetal (XI): a colorless oil, positive to an Ehrlich test; IR (film): 3400, 1685, 1650, 1245, 1110, 995 cm^{-1}; UV: λ_{max}^{MeOH} 250 nm (ε, 4500); NMR (CCl_4): 5.7—5.5 (two signals centered at 5.69 and 5.55, 1H), 5.4—5.1 (two signals centered at 5.32 and 5.12, 1H), 4.18 (OH), 1.88 (s, 13-CH_3), 0.93 (d, J=7.0 Hz, 14-CH_3), 0.78 and 0.70 (each s, 15-CH_3). This compound was found to afford isoligularone (XII) on glc (SF-96, 2.6 m; column temperature, 200 °C; H_2-flow rate, 60 ml/min).

b) By Sodium Borohydride. A crystalline mixture of hydroperoxides, VI-a, b (224.8 mg), was treated with sodium borohydride (73.4 mg) in methanol (14 ml) at room temperature for 19 hr. Subsequent working up as usual gave a crude product (230 mg), which was chromatographed on alumina (6 g, grade IV). Elution with benzene and benzene–ethyl acetate (30: 1) afforded petasalbin I (68 mg) and 6β-hydroxyeremophilenolide III (48 mg). The products, I and III, were identified by a comparison of the tlc and the IR spectra and by a mixed-melting-point determination with natural samples.

c) By a Platinum Catalyst. Hydroperoxide VI-a (202 mg) in acetic acid (4 ml) was hydrogenated over platinum oxide (52.6 mg) at room temperature until the hydrogen-uptake

had ceased (0.91 mol). After working up as usual, the chromatography of the crude product (175 mg) on silica gel (4 g) with benzene–ethyl acetate (50: 1 and 20: 1) gave 6β-hydroxy-8α-methoxyepieremophilenolide, VIII-a (34.4 mg); 6β-hydroxyeremophilenolide, III (6.1 mg), and 6β,8β-dihydroxyeremophilenolide, IV (43.7 mg). All the products were found to be identical with the authentic samples by a comparison of the tlc and the IR spectra and by a mixed-melting-point determination.

Isoligularone (XII)[11] *from Hemiacetal (XI).* A solution of hemiacetal XI (70 mg) in acetic anhydride (1.5 ml) was warmed at 90 °C for 1 hr. The reaction mixture was then diluted with water (3 ml) and extracted with ether. The ethereal extract was washed with a saturated sodium hydrogen carbonate solution and then water, and dried. The removal of the solvent gave a crystalline product, isoligularone XII (68 mg), which was crystallized from methanol as needles: mp 147.0—148.0 °C, $[\alpha]_D^{23}$ +39.0° (*c*, 0.98, $CHCl_3$); positive to a Zimmermann test; IR (KBr): 3125, 3060, 1660, 1547, 1280 cm^{-1}; UV: λ_{max}^{MeOH} 269 nm (ε, 5100); MS: *m/e* 232 (M^+), 175 (base peak); NMR ($CDCl_3$): 7.02 (q, *J*=1.5 Hz, 6-H), 2.86 (dd, *J*=18, 13 Hz, 9α-H), 2.16 (d, *J*=1.5 Hz, 13-CH_3), 1.28 (s, 15-CH_3), 0.91 (d, *J*=7.5 Hz, 14-CH_3); tlc: R_f, 0.50 (benzene–ethyl acetate, 15: 1).

Found: C, 77.50; H, 8.73%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

Oxidation of Hemiacetal (XI). Jones' reagent (0.15 ml)[13] was added to a solution of hemiacetal XI (80 mg) in acetone (3 ml) over a period of 15 min under ice-cooling. After stirring for a further 45 min, the excess reagent was decomposed with methanol (5 drops), diluted with water, and extracted with ether. The extract was then worked up in the usual manner to give a crude oil (66 mg), which was subsequently chromatographed on silica gel (2 g). Elution with light petroleum–benzene (1: 1) gave 8-oxoisoeremophilenolide XIV (47 mg), which was crystallized from isopropyl ether as colorless needles; mp 76.5—77.5 °C, $[\alpha]_D^{25}$ +31.5° (*c*, 0.73, $CHCl_3$); positive to a Zimmermann test; IR(KBr): 1760, 1695, 1195 cm^{-1}; UV: λ_{max}^{MeOH} 245 nm (ε, 7700); NMR (CCl_4): 5.42 (q, *J*=2.5 Hz, W1/2=5 Hz, 6-H), 3.63 (dd, *J*=16.5, 6.5 Hz, 9α-H), 1.92 (d, *J*=2.5 Hz, 13-CH_3), 1.05 (d, *J*=7.5 Hz, 14-CH_3), 0.79 (s, 15-CH_3); tlc: R_f, 0.66 (benzene–ethyl acetate, 10: 1).

Found: C, 72.39; H, 8.13%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

Ligularone (XIII).[1b,c] Compound XIII was prepared from petasalbin I (100 mg) by chromium trioxide (80mg) in pyridine (6.8 ml). The crude product was chromatographed on alumina (800 mg) and then crystallized from light petroleum to afford ligularone XIII as prisms: mp 66.0—67.5 °C, $[\alpha]_D^{25}$ −50.0° (*c*, 1.03, $CHCl_3$); tlc: R_f, 0.90 (benzene); (Found: C, 77.48; H, 8.87%). This compound was found to be identical with natural specimen by a comparison of the IR and NMR spectra and by a mixed-melting-point determination.

6-Oxoeremophilenolide (XV).[1-a] Jones' reagent (0.26 ml) was stirred over a period of 30 min under ice-cooling into a solution of 6β-hydroxyeremophilenolide III (148 mg) in acetone (5 ml). After stirring for a further 2 hr, the reaction mixture was worked up as has been described above to afford 6-oxoeremophilenolide XV (136 mg), which was subsequently crystallized from isopropyl ether as prisms: mp 124.0—126.0 °C, $[\alpha]_D^{24}$ −27.1° (*c*, 1.07, $CHCl_3$); IR(KBr): 1740, 1690, 1190, 1150, 1090, 1050, 930 cm^{-1}; UV: λ_{max}^{MeOH} 240 nm (ε, 11100); NMR (CCl_4): 4.88 (m, W1/2=21 Hz, 8-H), 1.85 (d, *J*=2.2 Hz, 13-CH_3), 1.11 (s, 15-CH_3), 0.63 (d, *J*=6.0 Hz, 14-CH_3); tlc: R_f, 0.75 (benzene–ethyl acetate, 10: 1).

Found: C, 72.51; H, 8.21%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

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References

1) a) L. Novotný, V. Herout, and F. Sorm, *Coll. Czech. Chem. Commun.*, **29**, 2189 (1964). b) H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, **21**, 2605 (1965). c) K. Naya, M. Nakagawa, M. Hayashi, K. Tsuji, and M. Naito, *Tetrahedron Lett.*, **1971**, 2961.

2) H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc.*, **1966**, 1545.

3) H. Nagano, Y. Tanahashi, Y. Moriyama, and T. Takahashi, This Bulletin, **46**, 2840 (1973).

4) L. Novotný, Z. Samek, and F. Sorm, *Coll. Czech. Chem. Commun.*, **31**, 371 (1966).

5) F. Sorm, *Pure Appl. Chem.*, **21**, 281 (1970).

6) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck, and K. H. Schulte-Elte, *Tetrahedron*, **23**, 2583 (1967).

7) G. O. Schenck, *Angew. Chem.*, **57**, 101 (1944), **69**, 579 (1957); E. Koch and G. O. Schenck, *Chem. Ber.*, **99**, 1984 (1966).

8) K. Naya, H. Takashina, M. Sawada, and R. Kanazawa, 15th Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Symposium Papers (1971), p. 87.

9) C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowwitz, *J. Amer. Chem. Soc.*, **84**, 870 (1962).

10) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco (1964), p. 110.

11) M. Tada and T. Takahashi, *Tetrahedron Lett.*, **1973**, 3999.

12) T. J. King and C. E. Newall, *J. Chem. Soc.*, **1962**, 367.

13) J. Mainwald, J. Crandall, and W. E. Hymans, "Organic Syntheses," Coll. Vol. V, p. 866 (1973).