CHEMISTRY LETTERS, pp. 1503-1506, 1979.

NEW SESQUITERPENE LACTONES FROM EUPATORIUM SACHALINENSE (FR. SCHMIDT) MAKINO

Kazuo ITO, Yoshihisa.SAKAKIBARA, and Mitsumasa HARUNA*

Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468

Three new germacranolide sesquiterpene lactones, peroxysachalinin, sachalinin, and sachalin, were isolated from Eupatorium sachalinense (Fr. Schmidt) Makino and their structures were described. An allyl hydroperoxy sesquiterpene lactone, peroxysachalinin, was characterized by spectral and chemical methods and prepared by photosensitized oxygenation of eupatoriopicrin which was a main component of this plant. Peroxysachalinin was converted to sachalinin with triphenylphosphine, whereas sachalinin was converted to sachalin.

In the continuing research for physiologically active sesquiterpene lactones of the Eupatorium species,$^{1)}$ we have examined the fresh whole plants of Eupatorium sachalinense (Fr. Schmidt) Makino.$^{2)}$ In the present paper, we wish to describe on the isolation and structure determination of three new germacranolides, peroxysachalinin (1), sachalinin (2), and sachalin (3). The allyl hydroperoxy sesquiterpene lactone, peroxysachalinin (1), was characterized by spectral and chemical methods and derived by photosensitized oxygenation of eupatoriopicrin (4)$^{3)}$ which is a main component of this plant. Peroxysachalinin (1) was transformed to sachalinin (2) by mild reduction with triphenylphosphine, whereas (2) was converted to sachalin (3) by alkaline hydrolysis.

The physical data of these three new sesquiterpene lactones are shown below.

Peroxysachalinin (1) as a colorless oil: $C_{20}H_{26}O_8$; $[\alpha]_D^{25}$ +123.4° (c=0.2, MeOH); UV (MeOH) 211 nm (ε=16,603); CD curve $[\theta]_{247}$ 0, $[\theta]_{260}$ -4363, $[\theta]_{293}$ 0 ; IR (KBr) 3450, 1760, 1716, 1670, and 1650 cm^{-1}; ^{1}H-NMR (cf. Table 1); ^{13}C-NMR (cf. Table 2)

Sachalinin (2) as a colorless oil: $C_{20}H_{26}O_7$; $[\alpha]_D^{25}$ +98.5° (c=0.2, MeOH); UV (MeOH) 211 nm (ε=16,927) ; CD curve $[\theta]_{248}$ 0, $[\theta]_{260}$ -3638, $[\theta]_{292}$ 0 ; IR (KBr) 3430, 1765, 1715, 1670, and 1650 cm^{-1} ; m/e 378 (M^+), 360 $(M-H_2O)^+$, 342 $(M-2 \times H_2O)^+$, 264 $(M-C_5H_7O_3+H)^+$, 246 $(M-C_5H_8O_4)^+$.

Sachalin (3) as a colorless oil: $C_{15}H_{20}O_4$; $[\alpha]_D^{25}$ +31.5° (c=0.2, MeOH); UV (MeOH) 210 nm (ε=12,138); CD curve $[\theta]_{218}$ 0, $[\theta]_{225}$ -5317, $[\theta]_{236}$ 0, $[\theta]_{260}$ -5696, $[\theta]_{290}$ 0 ; IR (KBr) 3450, 1750, and 1670 cm^{-1}; m/e 264 (M^+), 246 $(M-H_2O)^+$, and 228 $(M-2 \times H_2O)^+$.

Peroxysachalinin (1), on acetalization with acetone and p-toluenesulfonic acid, gave an acetonide (1a):[IR ($CHCl_3$) 3550, 3420, 1770, 1715, and 1660 cm^{-1}; m/e 434 (M^+), 418 $(M-O)^+$, 403, 360 $(M-O-Me_2CO)^+$, 358 $(M-H_2O-Me_2CO)^+$, 342 $(M-H_2O_2-Me_2CO)^+$, 317, 263 $(M-C_8H_{11}O_4)^+$, 246, and 228]. The ^{1}H-NMR spectrum of (1) showed peaks δ5.27 (1H, s.br, H-14), 5.09 (1H, s.br, H-14), and 10.6 (1H, s.br, -OOH, D_2O exchanged), while the ^{13}C-NMR spectrum contained twenty peaks, three of which, located at δ67.9 (C-8), 75.4 (C-6), and 89.9 (C-1), were assignable to oxygenated carbon except for the ester group. The peak at δ89.9 is uniquely characteristic of an allylic carbon bearing a hydroperoxy group.$^{4)}$ Furthermore, a ferrous thiocyanate test was positive.$^{5)}$

In order to obtain chemical evidence of the presence of an allylic hydroperoxy group in peroxysachalinin (1), the acetonide (1a) was converted with acetic anhydride and pyridine$^{6)}$ to keto deriva-

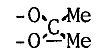
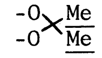
Table 1. ^{1}H-NMR spectra (99.6 MHz) of (1)-(3a)

Compd.	H-1	H-5	H-6	H-7	H-8	H-13	H-14	H-15	Miscellaneous
(1)^a	∿4.36^c	5.43dbr (10)	5.04t (10)	3.50m	5.88m	6.06d(3.5) 5.48d(3)	5.27sbr 5.09sbr	1.86sbr	6.93t(6,H-3'), 10.6sbr(OOH), 4.42d(6,H-4'), 4.32s(H-5')
(1a)^a	∿4.40^c	5.30dbr (9.5)	4.98t (9.5)	3.50m	5.85m	6.06d(3.5) 5.42d(3)	5.22s 5.04sbr	1.87sbr	6.92m(H-3'), 10.56s(OOH), 4.44;4.35m(H-4',5'), 1.36s(2 x acetal-CH_3)
(1b)^b	-	5.10dbr (9.5)	4.82dd (9.5;9)	2.88m	5.66m	6.26d(3.5) 5.54d^c	5.92s 5.54s^c	1.84sbr	6.82m(H-3'), 4.40;4.50m(H-4',5') 2.60dd(7.5;16,9-H), 3.12dd(3;16,9-H), 1.45s(2 x acetal-CH_3)
(2)^a	∿4.44^c	5.40dbr (9.5)	5.08t (9.5)	3.60m	5.90m	6.10d(3.5) 5.44d(3)	5.22s 4.96sbr	1.93sbr	6.92t(6,H-3'), 4.32s(H-5'), 4.40d(6,H-4')
(2a)^b	∿5.38^c	5.38^c	4.94^c	3.40m	5.80m	6.24d(3.5) 5.42d(3)	5.32s 4.94sbr	1.90sbr	6.80m(H-3'), 2.04s(OAc), 4.40;4.50m(H-4',5')
(3)^a	∿4.20m ($W_{\frac{1}{2}}$10)	5.46dbr (9.5)	4.96t (9.5)	3.23m	4.70m	6.15d(3.5) 5.60d(3)	5.12s 4.86sbr	1.88sbr	-------------------
(3a)^b	∿5.38^c	5.38^c	4.96^c	3.38m	5.80m	6.25d(3.5) 5.45d(3)	5.32s 4.97sbr	1.89sbr	2.02s(OAc), 2.06s(OAc)

a: Run in CD_3COCD_3 on a JEOL FX-100 spectrometer with Me_4Si as internal standard. Values are parts per million; s, singlet; d, doublet; t, triplet; m, multiplet; sbr, broad singlet; dbr, broad doublet; dd, doublet of doublets. Figures in parentheses are coupling constants in Hertz.

b: Run in $CDCl_3$. c: Signal partially obscured or superimposed.

Table 2. ^{13}C-NMR spectra (25.05 MHz) of lactones

Carbon atom	(4)^a	(1)^a	(2)^a	(3)^a	(1b)^b
1	130.4 d	89.9 d	76.6 d*	76.9 d*	203.1 s
2	26.2 t	28.4 t^{c*}	31.6 t^{c*}	33.4 t^{c*}	30.2 t^c
3	39.3 t	33.2 t^{c*}	33.3 t^{c*}	34.8 t^{c*}	34.4 t^c
4	134.1 s^e	149.2 s^{e*}	149.3 s^{e*}	149.4 s^{e*}	144.2 s^e
5	127.7 d	124.5 d*	124.5 d*	125.5 d*	124.8 d
6	75.8 d	75.4 d	75.5 d	75.2 d	74.3 d
7	52.7 d	48.2 d*	47.3 d*	49.1 d*	50.9 d
8	72.2 d	67.9 d	68.0 d	65.1 d	68.1 d
9	43.9 t	35.0 t^{c*}	34.5 t^{c*}	35.4 t^{c*}	38.1 t^c
10	141.6 s^e	143.9 s^{e*}	143.6 s^{e*}	142.3 s^{e*}	142.5 s^e
11	137.6 s	136.8 s	136.6 s	138.1 s	135.6 s
12	169.3 s	169.4 s	169.4 s	170.4 s	168.6 s
13	120.2 t	119.5 t	119.2 t	119.2 t	120.6 t
14	19.0 q	117.2 t*	113.4 t*	112.9 t*	126.8 t
15	17.1 q	17.7 q	17.9 q	18.1 q	17.2 q
1'	165.8 s	166.0 s	166.2 s	-	163.8 s
2'	131.8 s	131.9 s	132.1 s	-	132.3 s
3'	146.5 d	146.4 d	146.2 d	-	142.2 d
4'	58.8 t	58.8 t	58.8 t	-	60.7 t
5'	56.4 t	56.4 t	56.5 t	-	59.6 t
	-	-	-	-	102.3 s
	-	-	-	-	23.6 q

a: Run in C_5D_5N on a JEOL FX-100 spectrometer with Me_4Si as internal standard. s, singlet; d, doublet; t, triplet; q, quartet; *, broad signal. Assignment established by single frequency off-resonance decoupling and based on predicted shifts.

b: Run in $CDCl_3$.

c and e: Assignments may be interchanged.

tive (1b):[$C_{23}H_{28}O_7$; UV (MeOH) 211 nm (ε=17,148); IR ($CHCl_3$) 1770 (γ-lactone), 1715 (ester), and 1675 (α,β-unsaturated ketone); m/e 416 (M^+), 401, 358, 330, and 262].

Preparation of peroxysachalinin (1) was accomplished in good yield by photooxygenation[7] of eupatoriopicrin (4), a main component of this plant, by use of visible light and methylene blue as a sensitizer, thereby confirming the absolute structure of (1) except for the stereochemistry at C-1. The stereochemistry of the hydroperoxy group at C-1 was determined to be β-orientation as follow. Since the conformation in solution of eupatoriopicrin (4) as shown in (5) has been chemically related to epitulipinolide (5a)[3], which in turn has been related to costunolide (5b)[8] by their circular dichroism. Costunolide was shown to have two methyl groups oriented upwords and olefinic linkages crossed from NOE analysis.[9] The stereochemistry of singlet-oxygen addition has been established to proceed *via* a cis cyclic mechanism, with the oxygen approaching perpendicularly to the olefinic plane.[7] Thus, the hydroperoxy group in (1) must be placed at β-position. From above experiments and physical data, the structure of peroxysachalinin was established to be (1).

Sachalinin (2) and sachalin (3) are mutually related germacranolide sesquiterpene lactones. Acetalization of (2) with acetone and p-toluenesulfonic acid, followed by acetylation gave an acetate (2a):[IR ($CHCl_3$) 1770, 1725, and 1660 cm^{-1}; m/e 460 (M^+), 445, 402, 400, 360, 342, 288, 246, and 228]. Sachalinin (2) is similar to peroxysachalinin (1) in their spectral data, except for the ^{13}C-NMR signal due to C-1 carbon of (2). The mild reduction of (1) with triphenylphosphine afforded sachalinin (2).

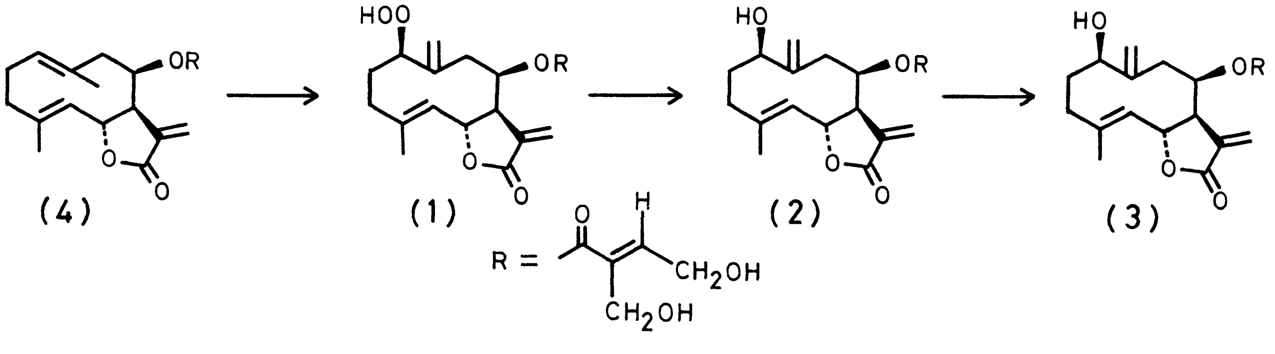
On the other hand, sachalin (3), on acetylation with acetic anhydride and pyridine, gave a diacetate (3a):[$C_{19}H_{24}O_6$; IR ($CHCl_3$) 1765, 1740, and 1660 cm^{-1}; m/e 348 (M^+), 306, 288, 264, and 246], the ^1H- and ^{13}C-NMR spectra of which were almost superimposable on those of (2a) except for the absence of the ester group. The alkaline hydrolysis of sachalinin (2) with 10% Na_2CO_3 in aqueous dioxane at room temperature afforded a diol, which was completely identical with sachalin (3).

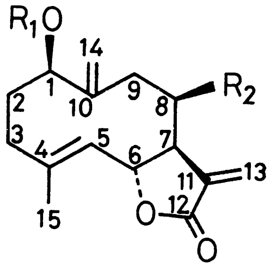
From above experiments, the structures of sachalinin and sachalin were clarified to be (2) and (3), respectively.

Prior to our isolation of peroxysachalinin (1) from this plant (*E. sachalinense*), three hydroperoxide sesquiterpene lactones from several Magnoliaceous plants were reported; namely peroxyferolide (6) from *Liliodendron tulipifera*,[6] and peroxycostunolide (7) and peroxypartenolide (8) from *Magnolia grandiflora*.[4]

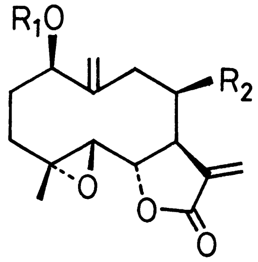
Therefore, peroxysachalinin (1) is the first sesquiterpene lactone hydroperoxide from plants of Compositae.

The co-occurrence of eupatoriopicrin (4), peroxysachalinin (1), sachalinin (2), and sachalin (3) in this plant is strongly indicative of their biosynthetic interrelationship, and transformation of (4) ⟶ (3) may proceed through the sequence of biogenetically feasible steps shown below.

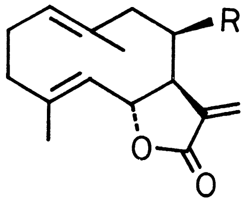




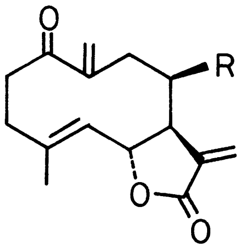
(1) R_1=OH, R_2= (A)
(1a) R_1=OH, R_2= (B)
(2) R_1=H, R_2= (A)
(2a) R_1=$COCH_3$, R_2= (B)
(3) R_1=H, R_2=OH
(3a) R_1=$COCH_3$, R_2=$OCOCH_3$
(7) R_1=OH, R_2=H



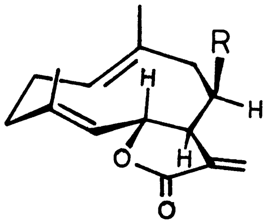
(6) R_1=OH, R_2=$OCOCH_3$
(8) R_1=OH, R_2=H



(4) R= (A)

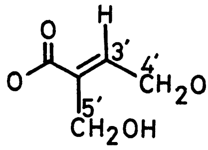


(1b) R= (B)

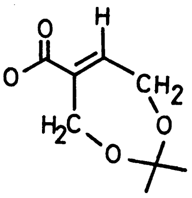


(5) R= (A)
(5a) R=OAc
(5b) R=H

(A) =



(B) =



REFERENCES AND NOTES

1) K. Ito, Y. Sakakibara, M. Haruna, and K. -H. Lee, Chem. Lett., 1979, 1469.
K. Ito, Y. Sakakibara, and M. Haruna, Chem. Lett., 1979, 1473.

2) Collected at Toubetsu, Hokkaido, Japan, August 1978.
cf. T. Takahashi, H. Eto, T. Ichimura, and T. Murae, Chem. Lett., 1978, 1345.

3) R. W. Doskotch and F. S. El-Feraly, J. Org. Chem., 35, 1928 (1970).

4) F. S. El-Feraly, Y. -M. Chan, E. H. Fairchild, and R. W. Doskotch, Tetrahedron Lett., 1973 (1977).

5) M. H. Abraham, A. G. Davis, D. R. Llewellyn, and E. M. Thain, Anal. Chem. Acta., 17, 499 (1976).

6) R. W. Doskotch, F. S. El-Feraly, E. H. Fairchild, and C. -T. Huang, Chem. Comm., 402 (1976).

7) R. W. Denny and A. Nickon in " Organic Reaction " Vol. 20, p. 133, Wiley, New York 1973.

8) CD curve : costunolide (5b),[3] $[\theta]_{220}$ +110,000, $[\theta]_{262}$ -6660; epitulipinolide (5a),[3] $[\theta]_{222}$ +146,000, $[\theta]_{264}$ -7180; eupatoriopicrin (4), $[\theta]_{220}$ +150,940, $[\theta]_{268}$ -5640.
From the above data, each ring conformation of (5b), (5a), and (4) is estimated to be the same in solution.

9) K. Tori, I. Horibe, Y. Tamura, and H. Tada, Chem. Comm., 620 (1973).

(Received August 7, 1979)