ピレスロイド類の代謝と化学反応性

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Original Article

Metabolism and Chemical Reactivity of Pyrethroids: Stereochemistry of the 7-Hydroxy Metabolite of (*S*)-Bioallethrin and the Chemical Oxidation of Rethronyl Acetates

Tetsu ANDO, Nozomu KOSEKI,* Tomoyuki KOKURYU, Kie KASUGA and Masahiro NATSUME

Department of Applied Biological Science, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Fuchu 183, Japan

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Alkenyl side chains in the alcohol moiety of natural pyrethroids and (*S*)-bioallethrin are easily oxidized by mixed function oxidases (mfo) and chemical oxidants, but the products have not been defined in detail. Thus, the absolute configuration of the 7-hydroxy derivative of (*S*)-bioallethrin, a major metabolite by mouse and rat liver microsomes, was examined by a modified Mosher's method which compared the ^{1}H NMR spectra of the esters with both enantiomers of α-methoxy-α-(trifluoromethyl)phenylacetic acid, and the (7*R*)-configuration was assigned for it indicating that the mfo attacked a (*pro-R*)-hydrogen at the 7-position of the pyrethroid. Further, oxidized products of the alcohol moieties by SeO_2 and *m*-chloroperoxybenzoic acid (MCPBA) were analyzed by NMR and GC-MS after their purification by HPLC. Both the regioselectivity of these reagents and their relative reactivity on the four different alkenyl side chains were similar to those of mammalian and insect mfo. This result indicated that SeO_2 and MCPBA oxidation could be used as a model reaction for metabolic studies of pyrethroids.

INTRODUCTION

The first synthetic pyrethroid, allethrin [(*S*)-bioallethrin (**1a**)], and the parent natural pyrethrins (**2a**, **3a** and **4a**) include alkenyl side chains in their alcohol moieties, which are easily oxidized by microsomal cytochrome P_{450}-dependent enzymes (mixed function oxidases, mfo) to produce hydroxy metabolites.[1-3] Among them, the 7-hydroxy derivative is one of the major components and acquires a new chiral center. Metabolic studies with mouse and rat liver microsomes revealed that the mfo oxidation at allylic 7-position proceeded stereoselectively, while two diastereomers of the 7-hydroxy derivative of **1a** were equivalently obtained *via* chemical oxidation of the propenyl side chain using selenium dioxide (SeO_2). Applying a modified Mosher's method,[4] we now report the absolute configuration of the metabolite to determine the surface attacked by the mfo. Another interesting point is the oxidative stability of the variant alkenyl side chains. Housefly killing activity of **2a**–**4a** was more significantly affected by a synergist, piperonyl butoxide (PB), than that of **1a**, suggesting that the alkenyl side chains of **2a**–**4a** were more easily metabolized than the propenyl group of **1a**.[5] This time we tried to define in detail oxidized products yielded by the reaction of rethronyl acetates with chemical oxidants SeO_2 and *m*-

* Present address: Central Research Laboratory, Kyorin Pharmaceutical Co., Ltd., Shimotsuga-gun, Tochigi 329-01, Japan

chloroperoxybenzoic acid (MCPBA) and to compare the chemical reactivity of the alkenyl side chains with their metabolic reactivity against mfo.

MATERIALS AND METHODS

1. *Chromatography*

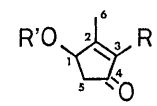
TLC utilized silica gel 60 F_{254} chromatoplates (0.25- and 0.5-mm layers) (Merck, Germany). HPLC, for analysis and separation of diastereomers, used a Yanaco L4000W Liquid Chromatograph equipped with a UV spectrometric detector (Shodex M-315), an integrator (Shimadzu C-R3A Chromatopac), and a Machrey-Nagel Nucleosil 5 NO_2 column (8 mm i.d. × 25 cm) packed by Senshu Kagaku Co. (Tokyo, Japan). The flow rate of the solvent, a mixture of tetrahydrofuran (THF) and *n*-hexane, was 2 ml/min and the eluent was monitored at 235 nm.

2. *Spectroscopy*

^{1}H NMR spectra (270.2 MHz) were recorded using a JEOL GX 270 Fourier transform spectrometer for $CDCl_3$ solution containing tetramethylsilane as an internal standard. Two-dimensional spectra of ^{1}H-^{1}H correlational spectroscopy (COSY) were measured using the same spectrometer with the usual pulse sequence.[6] Electron impact GC-MS was accomplished with a JEOL DX-300 gas chromatograph-mass spectrometer using an ionization voltage of 70 eV and a 1% OV-1 column (2.6 mm i.d. × 2 m). The ion source temperature was 150°C and column temperature was programmed (see Table 2).

3. *Chemicals*

The numbering system for rethronyl acetates and their derivatives is shown in Fig. 1. (1*R*)-*trans*-Chrysanthemic acid, (*SR*)-allethronyl acetate (**1b**), and the optically pure (*S*)-isomer of **1b** were supplied by Sumitomo Chemical Co., Ltd. (Osaka, Japan). Both (*S*)- and (*R*)-isomers of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, 99% pure) were purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI, U.S.A.), and all other chemical reagents were from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Cineronyl, jasmolonyl and pyrethronyl acetates (**2b**, **3b** and **4b**) were prepared from the racemic mixture **1b** according to published methods.[7]



	R': chrysanthemate of (1S)-isomer	R': acetate of (1SR)-isomer
R: (S)-bioallethrin	**1a**	**1b**
R: cinerin I	**2a**	**2b**
R: jasmolin I	**3a**	**3b**
R: pyrethrin I	**4a**	**4b**

Fig. 1 Chrysanthemates and acetates of four rethrolones with different side chains showing the numbering system used in this text.

4. *Synthesis of MTPA-ester of 7-Hydroxy-(S)-Bioallethrin*

By a published method,[8] (*S*)- and (*R*)-MTPAs were separately converted into (*R*)- and (*S*)-acid chlorides, respectively. Starting from SeO_2 oxidation of the (*S*)-isomer of **1b**, a diastereomeric mixture of 7-hydroxy-(*S*)-bioallethrin (**5a-i** and **-ii**) was synthesized by the same procedure previously described,[2] and the two diastereomers were separated by HPLC in a recyclic mode (five times) with solvent (20% THF in *n*-hexane); **5a-i**: *Rt* 51 min, $[\alpha]_D^{25} = -59°$ ($c = 0.70$, $CHCl_3$); **5a-ii**: *Rt* 56 min, $[\alpha]_D^{25} = +15°$ ($c = 0.74$, $CHCl_3$). The isomer with a shorter *Rt* (**5a-i**, 1.8 mg, 5.4 μmol) was treated with (*R*)-MTPA chloride (*ca.* 5 mg, 20 μmol), which had been prepared from (*S*)-MTPA, in pyridine (0.5 ml) at room temperature for 4 hr. The reaction mixture was poured into water (1 ml) and the crude product was extracted with ethyl acetate. The extract was washed with 1 N HCl and saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The (*S*)-MTPA ester (2.0 mg, 67% yield) was obtained after preparative TLC. The (*R*)-MTPA ester

of **5a-i** (2.2 mg, 74% yield) was prepared by coupling with (*S*)-MTPA chloride. Using another isomer with a longer *Rt* (**5a-ii**), the corresponding (*S*)-MTPA ester (2.4 mg, 81% yield) and (*R*)-MTPA ester (1.5 mg, 50% yield) were also obtained in the same manner. These four esters were then analyzed by ^{1}H NMR.

5. SeO_2 Oxidation of Rethronyl Acetates

SeO_2 (570 mg, 5.2 mmol) and **1b** (1 g, 5.2 mmol) were dissolved in a mixture of dioxane and water (10:1, 11 ml), and heated under reflux for 1 hr. The reaction mixture was then poured into water (10 ml) and crude products were obtained after usual workup. Preparative TLC gave **6** (13 mg, 1% yield), **5b** (290 mg, 27% yield) and **7** (130 mg, 12% yield) in addition to the recovery of **1b** (110 mg). Starting from **2b** (15 mg, 0.07 mmol), oxidized products **8** (1.1 mg, 7% yield), **9** (5.5 mg, 36% yield), **10** (2.0 mg, 13% yield) and **11** (1.2 mg, 8% yield), and the unreacted **2b** (4.0 mg) were obtained by a similar procedure.

To compare oxidation reactivity of the four rethronyl acetates, a mixture of **1b–4b** (0.5 mg each), SeO_2 (3 mg), dioxane (1 ml) and water (0.1 ml) was stirred at 90°C in a screw-capped vial. After 2 hr, another amount of SeO_2 (1.5 mg) was added to the mixture, which was further heated at 90°C for 2 hr. Every 30 min a trace of the mixture (10 μl) was taken out and diluted with HPLC solvent (10% THF in *n*-hexane, 1 ml). Its aliquot was injected into the HPLC column to quantitatively analyze unoxidized parts of the rethronyl acetates, which were completely separated by the mixed solvent as follows; *Rt* (min): **1b** 8.9, **2b** 8.3, **3b** 7.8, and **4b** 9.6. From these data, their oxidized parts and the relative reactivity of **2b–4b** compared to **1b** were calculated.

6. MCPBA Oxidation of Rethronyl Acetates

A mixture of MCPBA (>70%, 50 mg, 0.2 mmol) and **1b** (30 mg, 0.15 mmol) was stirred in CH_2Cl_2 (3 ml) at room temperature for 4 hr. After usual workup and preparative TLC, a diastereomeric mixture of 8,9-epoxy derivative **12** (26 mg, 80% yield) was obtained.[2] Under the same conditions, MCPBA oxidation of **2b** and **3b** produced the corresponding 8,9-epoxy derivatives, **13** and **14**, in *ca.* 75% yield. MCPBA oxidation of **4b** produced 8,9-epoxide **15** (49% yield) and 10,11-epoxide **16** (20% yield) under the same conditions.[3]

To compare the oxidation reactivity of the rethronyl acetates, a mixture of **1b–4b** (0.5 mg each), MCPBA (2 mg) and CH_2Cl_2 (1 ml) was stirred in a screw-capped vial at room temperature. After 1.5 hr, another amount of MCPBA (4 mg) was added to the mixture, which was further stirred at room temperature for 3 hr. Every 30 min a trace of the mixture (10 μl) was taken out and the oxidized quantity of each rethronyl acetate was analyzed by HPLC to estimate the relative reactivity against MCPBA in the same manner as for SeO_2 oxidation.

RESULTS AND DISCUSSION

1. Stereochemistry of 7-Hydroxy Metabolite of (S)-Bioallethrin

For determination of the absolute configuration of a secondary alcohol, Mosher's group developed a method utilizing the esters with both optically pure MTPAs.[8] The method was recently improved by Ohtani *et al.* to be applicable widely.[4] This advanced method is based on the hypothesis that the ester carbonyl and trifluoromethyl groups in the MTPA moiety and further the α-hydrogen in the secondary alcohol moiety are oriented on the same plane. An anisotropic effect by the benzene ring is expected to be observed on one of the two substituents at the α-carbon of the alcohol moiety in the (*S*)-MTPA ester, and on another in the (*R*)-MTPA ester. Thus, the stereochemistry is revealed by comparing their ^{1}H NMR spectra. By mouse and rat liver microsomes, oxidation at the 7-position of **1a** proceeded stereoselectively to produce secondary alcohol **5a-ii** with a longer *Rt* on a fused silica SPB5 capillary GC column and a normal phase NO_2 HPLC column.[2] To estimate the absolute configuration of this metabolite, we applied the advanced Mosher's method.

A diastereomeric mixture of the 7-hydroxy derivative (**5a-i** and **-ii**) was synthesized starting from the (*S*)-isomer of **1b**. After separating them by HPLC, four diastereomeric esters were separately prepared by combination with each of (*R*)- and (*S*)-MTPA chlorides

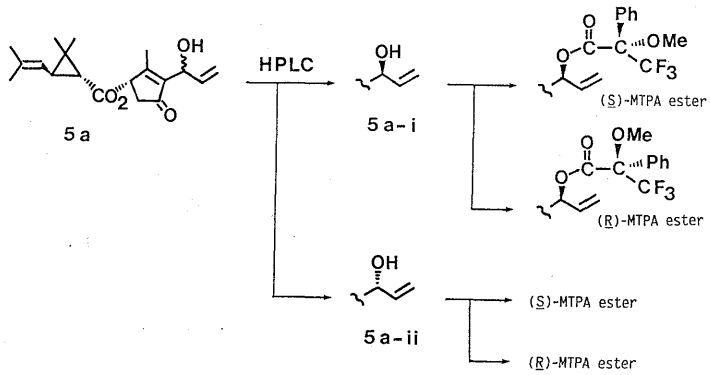


Fig. 2 Preparation of the MTPA esters of 7-hydroxy-(*S*)-bioallethrin (**5a-i** and **-ii**).

Table 1 ^{1}H chemical shift of the (*S*)-MTPA ester of 7-hydroxy-(*S*)-bioallethrin (**5a-i** and **5a-ii**) [δ_S], that of the (*R*)-MTPA ester [δ_R], and the difference [$\Delta\delta=\delta_R-\delta_S$].

Compound	^{1}H chemical shift (ppm) for indicated position[a)]							
	1	5α	5β	6	7	8	9c	9t
5a-i								
(*S*)-MTPA ester [δ_S]	5.673	2.295	2.888	2.075	6.325	5.939	5.254	5.315
(*R*)-MTPA ester [δ_R]	5.638	2.283	2.849	1.865	6.299	5.995	5.291	5.385
[$\Delta\delta=\delta_S-\delta_R$]	+0.035	+0.012	+0.039	+0.210	+0.026	−0.056	−0.037	−0.070
5a-ii								
(*S*)-MTPA ester [δ_S]	5.553	2.207	2.902	1.858	6.298	6.029	5.302	5.397
(*R*)-MTPA ester [δ_R]	5.640	2.258	2.920	2.052	6.317	5.960	5.266	5.330
[$\Delta\delta=\delta_S-\delta_R$]	−0.087	−0.051	−0.018	−0.194	−0.019	+0.069	+0.036	+0.067

a) The vinylidene protons *cis* and *trans* to H-8 are designated 9c and 9t, respectively.

(Fig. 2). ^{1}H NMR data of their alcohol moieties are shown in Table 1 together with the chemical shift difference ($\Delta\delta$) between the (*S*)-MTPA ester (δ_S) and (*R*)-MTPA ester (δ_R).

For MTPA esters of the shorter *Rt* isomer (**5a-i**), the $\Delta\delta$ values of the alkenyl side chain protons (H-8 and H-9) were negative and those of the 2-methylcyclopentenolone protons (H-1, H-5 and H-6) were positive. These data indicate that the alkenyl chain part in the (*S*)-MTPA ester and the pentene ring part in the (*R*)-MTPA ester are located on the same side of the benzene ring and accept its anisotropic effect, leading to the (7*S*)-configuration of **5a-i**. On the contrary, the (7*R*)-configuration was assigned to the longer *Rt* isomer (**5a-ii**), a major metabolite by mouse and rat liver microsomes, since the alkenyl chain protons of the (*R*)-MTPA ester and the pentene ring protons of the (*S*)-MTPA ester were more shielded than the others. This result theorized that the mfo attacked a (*pro-R*)-hydrogen at the 7-position of **1a**.

2. *SeO_2 Oxidation of Rethronyl Acetates*

Several oxidized compounds were isolated from the crude product mixture after SeO_2 oxidation of allethronyl acetate (**1b**) and cineronyl acetate (**2b**) by preparative TLC. Their chromatographic behavior, GC-MS data and ^{1}H NMR peak assignments are listed in Tables 2 and 3.

SeO_2 oxidation of **1b** yielded 7-keto derivative **6** and 9-hydroxy derivative **7** in addition to the major product **5b** which was previously characterized[2)] (see Fig. 3). Ketone **6** showed the highest mobility during silica gel chromatography and a molecular ion $[M]^+$ at *m/z* 208 in the mass spectrum. The NMR data well explained about the oxopropenyl side

Table 2 Chromatographic characteristics and GC-MS data of allethronyl acetate (**1b**), cineronyl acetate (**2b**), their SeO_2-oxidized products (**5b**, **6**–**11**) and some epoxy compounds (**12**–**14**).

Compound	TLC[a]	HPLC[b]	GC-MS				
				m/z (relative intensity)			
	Rf	*Rt* (min)	*Rt*[c] (min)	$[M]^+$	$[M-18]^+$	$[M-60]^+$	Base ion
1b	0.72	4.4	4.6	194 (4)		134 (91)	91
6	0.56	6.4	5.7	208 (14)		148 (80)	53
5b	0.50	8.2, 8.5	6.0	210 (2)	192 (4)	150 (100)	150
7	0.40	19.6	8.5	210 (4)	192 (2)	150 (100)	150
2b	0.72	4.3	4.0	208 (6)		148 (100)	148
8	0.56	7.6	4.8	222 (17)		162 (41)	69
9[d]	0.50	8.5	5.1		206 (10)	164 (14)	146
10	0.42	12.1, 12.5	6.2		206 (15)	164 (16)	146
11	0.32	20.6	6.7		206 (18)	164 (57)	146
12	0.54	5.8	6.4	210 (10)		150 (49)	106
13	0.56	5.6	5.6	224 (6)		164 (27)	106
14	0.56	7.0	6.3	238 (10)		178 (40)	106

[a] Silica gel chromatoplate with 33% acetone in *n*-hexane.
[b] Nucleosil 5 NO_2 column with 30% THF in *n*-hexane at a flow rate of 2 ml/min.
[c] The GC temperature was programmed from 100°C for 1 min, 16°C/min to 132°C, and finally 8°C/min to 188°C for **1b** and the oxidized products (**5b**, **6**, **7**, and **12**), and from 120°C for 1 min, 16°C/min to 152°C, and finally 8°C/min to 208°C for **2b**, the oxidized products (**8**–**11**, **13**), and **14**.
[d] Two diastereomers were separated by a solvent of 20% THF in *n*-hexane; *Rt* 13.5 and 14.3 min.

Table 3 Partial ^1H peak assignments of allethronyl acetate (**1b**), cineronyl acetate (**2b**), their SeO_2 oxidized products (**5b** and **6**–**11**) and some epoxy compounds (**12**–**14**).

Compound	^1H shift (ppm) for indicated position					Coupling constant (Hz)		
	6	7	8	9	10	J_{7-8}	J_{8-9}	J_{9-10}
1b	2.03	2.99	5.73	4.97, 4.99	—	6	10.5	—
6	2.27	—	6.94	5.93, 6.30	—	—	10.5, 17.5	—
5b[a]	2.06	5.00	6.00	5.18, 5.28	—	5.5	10.5, 17	—
7	2.11	6.34	7.02	4.33	—	16	5	—
2b	2.05	2.98	5.30	5.50	1.71	7	10.5	6.5
8	2.22	—	6.65	6.89	1.96	—	16	7
9[a,b]	2.05	~4.9	~5.7	~5.7	1.70	6	15	6
10[a]	2.10	6.29	6.94	4.44	1.34	16	6	6
11	2.03	2.99	~5.6	~5.6	~3.0	7	Unknown	Unknown
12[c,d]	2.08	2.45, ~2.6	3.05	~2.5, 2.76	—	7, 4.5	2.5, 4.5	—
13[a,e]	2.09	2.35, 2.57	3.02	3.08	1.37	7.5, 4.5	4.5	5.5
14[a,f]	2.09	2.31, 2.60	3.06	2.90	1.64	7.5, 4.5	4.5	6.5

[a] Diastereomer with the shorter *Rt* on a Nucleosil NO_2 HPLC column.
[b] Coupling constants were measured after acetylation of the hydroxyl group.
[c] Mixture of two diastereomer (1 : 1).
[d] J_{7-7}=14.5 Hz, J_{9-9}=5.5 Hz.
[e] J_{7-7}=14.5 Hz.
[f] J_{7-7}=14.5 Hz, H-11 1.07 ppm, J_{10-11}=7.5 Hz.

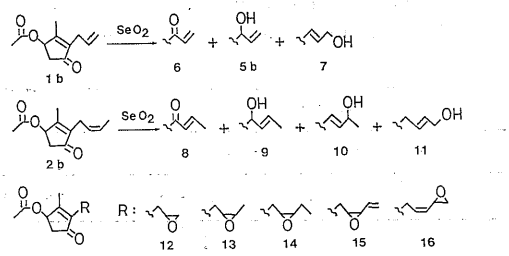


Fig. 3 Chemical structures of the oxidized products of rethronyl acetates by SeO_2 and MCPBA.

chain. Primary alcohol **7** was more polar than secondary alcohol **5b**. The COSY spectrum of **7** confirmed that the double bond at the 8-position in parent compound **1b** had migrated to the 7-position.

SeO_2 oxidation of **2b** also produced 7-keto derivative **8**, the most nonpolar component with an $[M]^+$ at *m/z* 222, and some hydroxy derivatives, **9–11**, with a fragment ion $[M-18]^+$ at *m/z* 206. A major component of the oxidized products was 7-hydroxy derivative **9**. Although two olefinic protons of **9** resonated in a similar magnetic field, the NMR spectrum of an acetylated derivative of **9** showed H-8 (5.71 ppm) and H-9 (5.79 ppm) separately and the coupling constant (15 Hz) between these protons indicated an (*E*)-configuration for the C=C double bond. A 7-hydroxy derivative persisting from the original (*Z*)-configuration could not be identified among the SeO_2-oxidized products. This configurational conversion was understood by a reaction mechanism proposed for the oxidation of allylic methylene.[9] Since the starting material **2b**, which was not contaminated with the (*E*)-isomer, was recovered after the SeO_2 oxidation, the (*Z*)-configuration of **2b** might be unconverted by heat and the selenium metal before the attack by selenious acid at the double bond, an initial step of the SeO_2 oxidation. COSY experiments on the two other hydroxy derivatives assigned secondary alcohol **10** with a migrated double bond for the less polar component, and primary alcohol **11** for the more polar component. An (*E*)-configuration of **11** was also possibly estimated from a mechanistic route of SeO_2 oxidation, but it could not be confirmed by NMR analyses.

3. *MCPBA Oxidation of Rethronyl Acetates*

MCPBA specifically oxidized the olefinic side chains of rethronyl acetates (**1b–4b**) to yield monoepoxy derivatives (**12–16**). Spectroscopic data are listed in Tables 2 and 3. Any compounds with the pentene ring attacked by MCPBA could not be found in the crude products. From the (*Z*)-alkenes, **2b** and **3b**, the corresponding *cis*-epoxides, **13** and **14**, with an adequate J_{8-9} value (4.5 Hz) were formed. Diene **4b** was converted to two monoepoxides, **15** and **16**. These ^1H NMR data were in good agreement with those of the epoxy derivatives of pyrethrin II previously reported.[3]

4. *Comparative Oxidation of Rethronyl Acetates*

The alkenyl side chains of rethronyl acetates (**1b–4b**) were regioselectively attacked by both SeO_2 and MCPBA synchronizing with time, but their reactivity was different as shown in Table 4. When the four rethronyl acetates were treated with SeO_2 in one vial and com-

Table 4 Oxidation reactivity of four rethronyl acetates (**1b–4b**) against chemical oxidants.

Compound	Oxidized %, (relative reactivity)			
	SeO_2 oxidation		MCPBA oxidation	
	1 hr	3 hr	2 hr	4 hr
Allethronyl acetate (**1b**)	19 (1.0)	35 (1.0)	25 (1.0)	29 (1.0)
Cineronyl acetate (**2b**)	25 (1.3)	44 (1.3)	47 (1.9)	81 (2.8)
Jasmolonyl acetate (**3b**)	22 (1.2)	49 (1.4)	47 (1.9)	85 (2.9)
Pyrethronyl acetate (**4b**)	39 (2.1)	72 (2.1)	43 (1.7)	66 (2.3)

petitively oxidized, **4b** reacted most easily while **1b** remained the longest. Reactivity of **2b** and **3b** against SeO_2 was almost the same. In the case of MCPBA oxidation, **1b** also remained the longest but **2b** and **3b** were more easily attacked than **4b**. Consequently, the propenyl side chain in synthetic pyrethroid allethrin (**1a**) was more stable against both of the reagents than the other alkenyl groups in the natural pyrethroids, and the pentadienyl group in the most active insecticide pyrethrin I (**4a**) is more unstable against SeO_2 oxidation than the butenyl group in cinerin I (**2a**) and the pentenyl group in jasmolin I (**3a**). Opposite reactivity, however, was observed during MCPBA epoxidation among the three natural-type side chains.

5. Microsomal Oxidation vs. Chemical Oxidation

When (*S*)-bioallethrin (**1a**) and natural pyrethroids (**2a**–**4a**) were incubated with the microsomes prepared from mouse and rat liver, the doubly allylic position in the side chains of the rethronyl moieties was easily oxidized to produce the corresponding 7-hydroxy metabolites.[2] Experiments with **1b** and **2b** showed that chemical oxidant SeO_2 also readily attacked the 7-position, while the (*Z*)-double bond in **2b** was converted to an (*E*)-double bond in **9** by the SeO_2 oxidation. Configurations of the double bonds at the 8-position in 7-hydroxy metabolites of **2a**–**4a** are still unknown. The SeO_2 oxidation produced some minor products with a migrated double bond from the 8-position which had not been recognized as a metabolite. On the other hand, the mammalian mfo directly attacked the double bonds in the side chains and produced 8,9-dihydroxy metabolites of **1a**–**4a** and a 10,11-dihydroxy metabolite of **4a** *via* the corresponding epoxy intermediates.[3] Another chemical oxidant MCPBA also specifically attack the double bonds in the side chains of **1b**–**4b** but not in the pentene rings. Regioselectivity of the mfo and these chemical reagents was quite similar. The pyrethroids (**1a**–**4a**) are chiral compounds and expected to be in a stable conformation. Enzymatic oxidation proceeded stereoselectively, but SeO_2 and MCPBA, rather small reagents, approached the side chains from both sides equally and produced diastereomeric mixtures.

Microsomal oxidation is inhibited by PB, a synergist of pyrethroids. As reported in a previous paper, we compared the insecticidal activities of the four pyrethroids with different side chains using houseflies pretreated with and without PB. The most tenuous synergistic effect of this inhibitor had been observed on **1a** among the four compounds, indicating that **1a** was most moderately oxidized by the mfo of houseflies.[5] In this study the propenyl side chain of **1b** was not easily oxidized by both reagents of SeO_2 and MCPBA. Housefly killing activity of **4a** was significantly increased by PB suggesting the easiest metabolism of the pentadienyl side chain. The corresponding acetate **4b** showed the highest reactivity against SeO_2 among the natural type rethronyl acetates, but rather low reactivity against MCPBA. Although oxidation reactivity of the alkenyl side chains against mfo was not perfectly coincident with that against the chemicals, these results indicated that SeO_2 and MCPBA oxidation could be used as a model reaction for metabolic studies of pyrethroids.

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要　約

ピレスロイド類の代謝と化学反応性：(*S*)-ビオアレスリンの7位水酸化代謝物の立体化学とレスロニルアセテート類の化学酸化

安藤　哲，小関　望，国立朋之
春日紀恵，夏目雅裕

天然ピレスロイドおよび(*S*)-ビオアレスリンのアルコール側アルケニル側鎖は，混合機能オキシダーゼ(mfo)や化学試薬により容易に酸化されることが知られているが，その詳細については未だ不明なところがある．今回，光学活性なMTPAエステルの^{1}H NMRデータを比較する改良Mosher法を適用して，(*S*)-ビオアレスリンの7位水酸化代謝物は(7*R*)の立体配置を有すること，すなわちmfo(マウスおよびラット由来)は7位(*pro-R*)の水素原子を攻撃することを明らかにすることができた．また，レスロニルアセテート類のSeO_2あるいはMCPBAによる酸化物を，HPLCにて精製単離後NMRおよびGC-MS分析により同定しmfoによる酸化代謝物と比較したところ，SeO_2やMCPBAの示した位置選択性と4種のアルケニル側鎖に対する反応性はそれら哺乳動物や昆虫のmfoと類似しており，これらの酸化剤はピレスロイド類の代謝研究のためのモデル反応に利用可能であることが示された．