Original Article

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

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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 ¹H NMR spectra of the esters with both enantiomers of α -methoxy- α -(trifluoromethyl)phenylacetic acid, and the (7R)-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 SeO₂ 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 SeO₂ 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 (SeO₂). 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 SeO2 and m-

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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 F254 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 а Machrey-Nagel Nucleosil 5 NO2 column (8 mm i.d. \times 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

¹H NMR spectra (270.2 MHz) were recorded using a JEOL GX 270 Fourier transform spectrometer for CDCl₃ solution containing tetramethylsilane as an internal standard. Two-dimensional spectra of ¹H-¹H 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. \times 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. (1R)-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 ace-



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

tates (2b, 3b and 4b) were prepared from the racemic mixture 1b according to published methods.⁷⁾

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, $[\alpha]_{D}^{25} = -59^{\circ} (c = 0.70, \text{ CHCl}_{3});$ **5a-ii**: Rt 56 min, $\alpha_{\rm D}^{25} = +15^{\circ} (c = 0.74, \text{ CHCl}_{\rm s}).$ The isomer with a shorter Rt (**5a-i**, 1.8 mg, 5.4 μ mol) was treated with (R)-MTPA chloride (ca. 5 mg), 20 μ mol), 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 x HCl and saturated aqueous NaHCO₃ solution, dried over anhvdrous Na₂SO₄ 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 ¹H NMR.

5. SeO₂ Oxidation of Rethronyl Acetates

SeO₂ (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), SeO₂ (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 SeO₂ (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 μ l) 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 CH₂Cl₂ (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.⁸⁾

To compare the oxidation reactivity of the rethronyl acetates, a mixture of 1b-4b (0.5 mg each), MCPBA (2 mg) and CH₂Cl₂ (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 μ l) 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 SeO₂ 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 ¹H NMR spectra. By mouse and rat liver microsomes, oxidation at the 7-position of la proceeded stereoselectively to produce secondary alcohol **5a-ii** with a longer Rt on a fused silica SPB5 capillary GC column and a normal phase NO₂ 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

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

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

		¹ H c	hemical s	hift (ppn	n) for indi	cated pos	sition ^{a)}	
Compound	1	5α	5 <i>β</i>	6	7	8	9c	9t
5a-i (S)-MTPA ester $[\delta_S]$ (R)-MTPA ester $[\delta_R]$	5.673 5.638	2.295 2.283	2.888 2.849	2.075 1.865	6.325 6.299	5.939 5.995 0.056	5.254 5.291 -0.037	5.31 5.38 -0.070
$\begin{bmatrix} \Delta \delta = \delta_S - \delta_R \end{bmatrix}$ 5a-ii (S) MTPA ester $\begin{bmatrix} \delta_R \end{bmatrix}$	+0.035	+0.012	+0.039 2.902	+0.210	6.298	6.029	5.302	5.39
(S)-MTPA ester $[\delta_R]$ (R)-MTPA ester $[\delta_R]$ $[\Delta \delta = \delta_S - \delta_R]$	5.640 0.087	2.258 -0.051	$2.920 \\ -0.018$	2.052 -0.194	6.317 - 0.019	5.960 + 0.069	5.266 + 0.036	5.33 +0.06

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

(Fig. 2). ¹H 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 (7S)-configuration of 5a-i. On the contrary, the (7R)-configuration was assigned to the longer Rt isomer (5aii), 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. SeO₂ Oxidation of Rethronyl Acetates

Several oxidized compounds were isolated from the crude product mixture after SeO₂ oxidation of allethronyl acetate (**1b**) and cineronyl acetate (**2b**) by preparative TLC. Their chromatographic behavior, GC-MS data and ¹H NMR peak assignments are listed in Tables 2 and 3.

SeO₂ oxidation of **1b** yielded 7-keto derivative **6** and 9-hydroxy derivative **7** in addition to the major product **5b** which was previously characterized²⁾ (see Fig. 3). Ketone **6** showed the highest mobility during silica gel chromatography and a molecular ion $[M]^+$ at m/z208 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 SeO₂-oxidized products (5b, 6-11) and some epoxy compounds (12-14).

Compound TLC:					GC-MS		<u> </u>
	TLC ^a)	HPLC ^{b)}		m/z (relative intensity)			
	Rf	Rt (min)	Rt^{c} (min)	[M]+	[M -18]+	$[M - 60]^+$	Base ion
1 b	0.72	4.4	4.6	194 (4)		194 (01)	
6	0.56	6.4	5.7	208 (14)		134 (91)	91
5 b	0.50	8.2.8.5	6.0	210(11)	109 (4)	148 (80)	53
7	0.40	19.6	8.5	210(2)	192(4)	150 (100)	150
2 b	0.72	4.3	4 0	210(-1)	192 (2)	150 (100)	150
8	0.56	7.6	4.8	200(0)		148 (100)	148
9 d)	0.50	8.5	5 1	222 (17)	906 (10)	162 (41)	69
10	0.42	12 1 12 5	5.1		206 (10)	164 (14)	146
11	0.32	20.6	6.7		206 (15)	164 (16)	146
12	0.54	5.9	0.7	010 (10)	206 (18)	164 (57)	146
13	0.54	J.0 E.C	6.4	210 (10)		150 (49)	106
14	0.56	5.6	5.6	224 (6)		164 (27)	106
+ ±	0.36	7.0	6.3	238 (10)		178 (40)	106

a) Silica gel chromatoplate with 33% acetone in *n*-hexane.

b) Nucleosil 5 NO₂ column with 30% THF in *n*-hexane at a flow rate of 2 ml/min.

*) 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.

Com-		¹ H shift (p	pm) for in	Coupling constant (Hz)				
pound	6	7	8	9	10	J ₇₋₈	J ₈₋₉	J9-10
1 b	2.03	2.99	5.73	4,97,4,99		6	10.5	
6	2.27		6.94	5.93, 6.30			10.5	
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	\sim 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°,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

Table 3 Partial ¹H peak assignments of allethronyl acetate (1b), cineronyl acetate (2b), their SeO₂ oxidized products (5b and 6-11) and some epoxy compounds (12-14).

^{a)} Diastereomer with the shorter Rt on a Nucleosil NO₂ HPLC column.

^{b)} Coupling constants were measured after acetylation of the hydroxyl group.

e) 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.

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Fig. 3 Chemical structures of the oxidized products of rethronyl acetates by SeO₂ 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 8position in parent compound **1b** had migrated to the 7-position.

SeO2 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 A 7-hydroxy derivative C=C double bond. persisting from the original (Z)-configuration could not be identified among the SeO2-This configurational conoxidized products. version 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 SeO2 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 SeO₂ 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 SeO₂ 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 SeO₂ and MCPBA synchronizing with time, but their reactivity was different as shown in Table 4. When the four rethronyl acetates were treated with SeO₂ in one vial and com-

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

Compound –	Oxidized $\frac{0}{0}$, (relative reactivity)				
	SeO ₂ ox	idation	MCPBA oxidation		
	1 hr	3 hr	2 hr	4 hr	
Allethronyl acetate (1h)	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)	
Lasmolonyl acetate (3b)	22(1,2)	49 (1.4)	47 (1.9)	85 (2.9)	
Pvrethronyl 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 SeO₂ 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 SeO₂ 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 naturaltype 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 SeO2 also readily attacked the 7-position, while the (Z)-double bond in 2b was converted to an (E)-double bond in 9 by the SeO₂ oxidation. Configurations of the double bonds at the 8-position in 7-hydroxy metabolites of 2a-4a are still unknown. The SeO₂ 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 8,9dihydroxy metabolites of 1a-4a and a 10,11dihydroxy 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 SeO2 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 la among the four compounds, indicating that **la** was most moderately oxidized by the mfo of houseflies.⁵⁾ In this study the propentyl side chain of **1b** was not easily oxidized by both reagents of SeO₂ 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 SeO₂ 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 SeO2 and MCPBA oxidation could be used as a model reaction for metabolic studies of pyrethroids.

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REFERENCES

- M. Elliott, N. F. Janes, E. C. Kimmel & J. E. Casida: J. Agric. Food Chem. 20, 300 (1972)
- T. J. Class, T. Ando & J. E. Casida: J. Agric. Food Chem. 38, 529 (1990)
- T. Ando, R. F. Toia & J. E. Casida: J. Agric. Food Chem. 39, 606 (1991)
- I. Ohtani, T. Kusumi, M. O. Ishitsuka & H. Kakisawa: Tetrahedron Lett. 30, 3147 (1989)
- T. Ando, L. O. Ruzo, J. L. Engel & J. E. Casida: J. Agric. Food Chem. 31, 250 (1983)
- T. Ando, M. Aburatani, N. Koseki, S. Asakawa, T. Mouri & H. Abe: Magn. Reson. Chem. 31, 94 (1993)
- T. Ando & J. E. Casida: J. Agric. Food Chem. 31, 151 (1983)
- J. A. Dale, D. L. Dull & H. S. Mosher: J. Org. Chem. 34, 2543 (1969)
- H. O. House: "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, Inc., Menlo Park, California, 1972

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

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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¹H 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(7R)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SeO2 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、SeO2 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.