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Insecticidal Activity of Streptothricin Antibiotics

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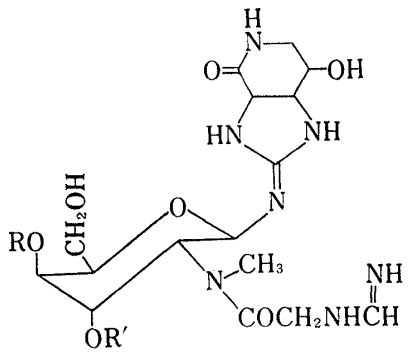
Racemomycin-A, -C and -B, like racemomycin-D, exhibited insecticidal activity against the adults of *Blattella germanica* and *Musca domestica*. These racemomycin compounds, like racemomycin-D, also showed a delayed toxicity on the adult of *Blattella germanica*. The insecticidal effect of racemomycin-A, -C and -B on both insects was in the order of B>C>A. As the number of β-lysine residues increased, the antibacterial effect increased along with the insecticidal effect. However, racemomycinic A acid, produced by opening of the lactam ring of the streptolidine moiety of racemomycin-A, showed no insecticidal effect. This would suggest an intimate relationship between the streptolidine moiety in the molecule of streptothricin antibiotics and the activity.

Citromycin, a streptothricin-like antibiotic, also exhibited an insecticidal effect against the adults of *Blattella germanica* and *Musca domestica*, like racemomycin series compounds.

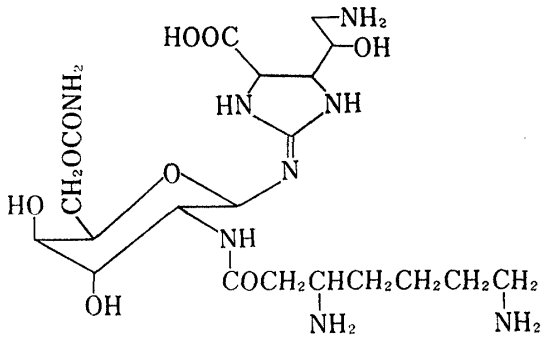
Keywords——insecticidal activity; racemomycin-A; racemomycin-C; racemomycin-B; racemomycinic A acid; citromycin; delayed insecticidal effect; streptolidine moiety

Racemomycin-D is a streptothricin antibiotic containing four β-lysine residues within the molecule. In addition to the antimicrobial activity so far described, this compound was reported by the authors[1] to have physiological actions such as insecticidal effect, fish-toxicity and inhibitory activity on plant growth. No insecticidal effect, however, has been reported for other racemomycin compounds such as racemomycin-A, -C and -B.

In the present study, the authors examined the insecticidal effect of streptothricin antibiotics, including racemomycin series compounds, as reported below.



R=H, R′=$CONH_2$ or R=$CONH_2$, R′=H
citromycin



racemomycinic A acid

Fig. 1. Chemical Structures of Citromycin and Racemomycinic A Acid

Materials and Methods

Chemicals——Racemomycin-A, -C and -B,[2] streptothricin antibiotics produced by *Streptomyces lavendulae* OP-2[3] were used. These antibiotics contain 1 to 3 β-lysine residues in one molecule. Citromycin[4] (Fig. 1) was supplied by Kaken Chemical Co., Ltd. Racemomycinic A acid (Fig. 1) was prepared from racemomycin-A according to the method of Taniyama *et al.*[5]

Insects——Adults of *Blattella germanica* and *Musca domestica* were used.

Insecticidal Activity Test——As described previously, the bait method[1] was used.

Temperature——Every experiment was carried out at 25—27°C.

Results

Insecticidal Activity of Racemomycins and Racemomycinic A Acid

As shown in Tables I and II, racemomycin-A, -C and -B, like racemomycin-D, exhibited insecticidal activity against the adults of *Musca domestica* and *Blattella germanica*.

Table I. Insecticidal Activity of Racemomycins on Adults of *Musca domestica*

Antibiotic	% mortality (ppm)		
	1000	500	100
Racemomycin-A	30	20	10
Racemomycin-C	50	30	20
Racemomycin-B	80	40	30
Control	0	0	0

Method of treatment: bait.
Observation time: 48 h.
Experimental size: 10 insects/group, 2 groups.
Temperature: 26°C.

The time courses of the effects of racemomycin-A, -C and -B on *Blattella germanica* are shown in Table II. These racemomycins, like racemomycin-D,[1] exhibited a delayed insecticidal effect.

Table II. Time Course of Mortality of *Blattella germanica* baited with Racemomycins

Antibiotic	Dose (ppm)	Number of dead (in 10 insects) at indicated time (h) after baiting				
		24	48	72	96	120
Racemomycin-A	100	0	0	0	0	0
	500	0	0	1	2	3
	1000	0	0	3	3	6
Racemomycin-C	100	0	0	0	0	0
	500	0	0	1	3	5
	1000	0	0	1	4	9
Racemomycin-B	100	0	0	1	1	1
	500	0	0	1	3	4
	1000	0	0	3	5	10
Control	0	0	0	0	0	0

Temperature: 26C°.
Experimental size: 10 insects/group, 2 groups.

The insecticidal effect on both insects was in the order of B>C>A, becoming more powerful as the number of β-lysine residues increased. In contrast, racemomycinic A acid, in

which the lactam ring of the streptolidine moiety is opened, was entirely devoid of insecticidal effect on the two insects.

Insecticidal Activity of Citromycin

In view of the insecticidal effect of racemomycins on the adults of *Blattella germanica* and *Musca domestica* as demonstrated by the bait method, the insecticidal effect of citromycin, one of the streptothricin–like antibiotics, on these two insects was studied by the bait mehod. The results are shown in Tables III and IV. Like racemomycins, citromycin showed insecticidal activity against the adults of *Blattella germanica* and *Musca domestica*.

TABLE III. Insecticidal Activity of Citromycin on Adults of *Musca domestica*

Antibiotic	% mortality (ppm)		
	1000	500	100
Citromycin	60	30	20
Control	0	0	0

Observation time: 48 h.
Method of treatment: bait.
Experimental size: 10 insects/group, 2 groups.
Temperature: 26°C.

As shown in Table IV, citromycin also showed a delayed insecticidal effect on the adults of *Blattella germanica*, like racemomycins.

TABLE IV. Time Course of Mortality of *Blattella germanica* baited with Citromycin

Antibiotic	Dose (ppm)	Number of dead (in 10 insects) at indicated time (h) after baiting				
		24	48	72	96	120
Citromycin	100	1	1	1	1	1
	500	1	4	4	4	5
	1000	1	4	4	10	10
Control		0	0	0	0	0

Temperature: 26°C.
Experimental size: 10 insects/group, 2 groups.

Discussion

The insecticidal effect was found to be greatest in the case of racemomycin-B, followed by racemomycin-C and then by racemomycin-A (Tables I and II). The increase of the antibacterial activity of racemomycins with increase in the number of β-lysine residues was already reported by Taniyama *et al.*[6] Racemomycin-D, containing four β-lysine residues in the molecule, shows greater insecticidal[1] and antibacterial[2] activity, than racemomycin-B. This would indicate that the β-lysine moiety in the molecule plays some role in the activity of streptothricin antibiotics, and further studies are necessary. In view of the absence of insecticidal action of racemomycinic A acid, the streptolidine moiety in the molecule of streptothricin appeared to play an important role in the activity of streptothricin antibiotics. Taniyama *et al.*[5] have already reported that racemomycinic A acid shows no antibacterial activity. These two facts strongly suggest an intimate relationship between the lactam ring of the streptolidine moiety of the streptothricin antibiotic and its activity.

Racemomycin-A, -C and -B showed delayed insecticidal effect against the adults of *Blattella germanica* (Table II). The delayed toxicity of streptothricin antibiotics on mammals is well known.

This would suggest a similarity in the mechanisms of toxicity of streptothricin antibiotics against insects and mammals. In fact, the authors demonstrated the accumulation of racemomycin-D in the Malpighian vessel of the 5th instar larvae of *Bombyx mori*.[7] In mammals, the authors have also demonstrated the distribution of large amounts of racemomycin-D to the kidneys of the rat and mouse,[8,9] causing severe nephrotoxicity.[10] The time of appearance of delayed toxicity of racemomycin-D, moreover, was found to be approximately the same in insects and mammals.[2] Such similarity of drug action between mammals and insects is of profound interest.

Citromycin, like racemomycins, showed insecticidal activity against the adults of *Blattella germanica* and *Musca domestica* (Tables III and IV). As shown in Fig. 1, however, citromycin is a streptothricin-like antibiotic containing formiminoglycine instead of β-lysine within the molecule, unlike racemomycins. The insecticidal effect of citromycin closely resembles that of racemomycins, since the compound exhibits delayed toxicity against the adults of *Blattella germanica* (Table IV). However, it is premature to conclude that all streptothricin–like antibiotics have insecticidal effect based on the test on citromycin alone, and many more tests on the insecticidal activity of other streptothricin-like antibiotics are required. However, the insecticidal effect of streptothricin antibiotics may represent a characteristic physiological activity for the following two reasons. 1) All racemomycins tested and citromycin showed insecticidal action. 2) Such insecticidal action is delayed.

Further studies are in progress.

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