Short Communication

Induction of Precocious Metamorphosis by 1,5-Disubstituted Imidazoles with a Non-terpene Chain

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We have already reported the anti-juvenile hormone (anti-JH) activity of a number of 1,5-disubstituted imidazoles with a JH-like terpene chain in silkworm, *Bombyx mori*, larvae.^{1,2)} These imidazole compounds induced unequivocal precocious metamorphosis, which was clearly recognized as a JH-deficiency symptom.³⁾ Two representative compounds, namely 1-citronellyl-5-phenylimidazole (KK-22) and 1-benzyl-5-[(E)-2,6-dimethyl-1,7-heptadienyl]imidazole (KK-42), have so far been found to show marked activity by topical and feeding applications.

On the other hand, Yamashita *et al.* have recently reported that KK-42 inhibited ecdysteroid synthesis in the prothoracic glands of *B. mori* *in vitro*, and consequently, ecdysteroid titers in the hemolymph of larvae and pupae treated with KK-42 were remarkably reduced.^{4,5)} They have suggested that the temporary inhibition of ecdysteroid secretion also induced precocious metamorphosis, since the delayed secretion of ecdysteroid can provide a hormonal milieu inducing larval-pupal metamorphosis in *B. mori*.⁶⁾ Roussel *et al.* have also found that KK-42 depressed the total amount of ecdysteroid release by the prothoracic glands of *Locusta migratoria* *in vitro*.⁷⁾ These facts prompted us to examine further structure-activity relationships of 1,5-disubstituted imidazoles. We consequently found

that imidazoles having a non-terpene substituent such as 1-neopentyl-5-(2-ethoxyphenyl)imidazole (KK-110) and 1-neopentyl-5-(4-chlorophenyl)imidazole (KK-135) induced precocious metamorphosis in *B. mori* larvae at low doses.

These 1,5-disubstituted imidazoles were prepared by two different procedures using tosylmethylisocyanide (TosMIC) according to methods described by van Leusen: (a) the reaction of the corresponding aldimines with TosMIC;⁸⁾ (b) the reaction of aliphatic amines with 1-isocyano-1-tosyl-1-alkenes, which are the dehydration products of the *N*-(1-tosyl-1-alkenyl)formamides obtained by the reaction of TosMIC with the corresponding alde-

TABLE I. INDUCTION OF PRECOCIOUS METAMORPHOSIS IN THE SILKWORM (GUNPO × SHUGYOKU) BY 1-SUBSTITUTED-5-PHENYIMIDAZOLES

No.	R	Precocious metamorphosis (%)	
		20	10 (μg/larva)
1	-CH ₂ C ₆ H ₅	0	
2	-(CH ₂) ₂ C ₆ H ₅	0	
3	-CH ₂ CH(CH ₃) ₂	90	70
4	-(CH ₂) ₃ CH ₃	70	10
5	-CH ₂ C(CH ₃) ₃	100	90
6	-CH ₂ CH ₂ C(CH ₃) ₃	20	0
	citronellyl (KK-22)	100	80

TABLE II. INDUCTION OF PRECOCIOUS METAMORPHOSIS IN THE SILKWORM (GUNPO × SHUGYOKU) BY 1-NEOPENTYL-5-SUBSTITUTED IMIDAZOLES

No.	R	Precocious metamorphosis (%)	
		4	2 (μg/larva)
5	H	—	0
7	2-OCH ₃	100	75
	2-OC ₂ H ₅ (KK-110)	100	75
8	3-OC ₂ H ₅	0	
9	4-OC ₂ H ₅	20	0
10	2-Cl	0	
11	3-Cl	5	0
	4-Cl (KK-135)	95	75

TABLE III. INDUCTION OF PRECOCIOUS METAMORPHOSIS IN THE SILKWORM BY IMIDAZOLE COMPOUNDS

Compound	ED ₅₀ (μg/larva)	
	C.137 × N.137	Kinshu × Showa
KK-110	1.6	1.6
KK-135	2.1	1.8
KK-42	0.4	0.4
KK-22	2.8	—

hydes.⁹⁾ The compounds in an acetone solution (1~4 μl/larva) were applied topically to newly molted 4th instar larvae of *B. mori* (Gunpo × Shugyoku, C.137 × N.137 and Kinshu × Showa). The activity was evaluated by the induction of precocious metamorphosis: spinning a cocoon and pupation in the 4th instar (penultimate) period.

Bioassay data are presented in Table I for a few representative examples of 1-substituted-5-phenylimidazoles. The compound containing a neopentyl group (5) showed an activity comparable to KK-22. The 3,3-dimethylbutyl analog (6) had considerably lower activity than the isobutyl (3) or *n*-butyl (4) analog. The benzyl (1) and phenethyl (2) analogs were inactive at 20 μg. The bioassay data for the 1-neopentyl-5-arylimidazoles are given in Table II. The introduction of a methoxy (7) or ethoxy (KK-110) substituent at the 2-position on the benzene ring increased the activity, and the 3- and 4-ethoxyphenyl (8 and 9) analogs showed comparatively low activity, while the 4-chlorophenyl analog (KK-135) showed higher activity than the 2- and 3-chlorophenyl analogs (10 and 11). Thus, in this series of imidazoles with a non-terpene chain, KK-110 and KK-135¹⁰⁾ were found to show higher

activity than KK-22, and there was little difference in activity between KK-110 and KK-135 on two strains of *B. mori* (Table III). Although these compounds were somewhat less active in comparison with KK-42, which has been the most effective of the imidazole compounds so far tested on *B. mori*, this new series of imidazoles as well as KK-42 might hold promise as insect growth regulators which can block JH or ecdysteroid actions.

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- 10) KK-110: mp 76~78°C. NMR (CDCl₃) δ: 0.72 (9H, s), 1.30 (3H, t, *J* = 7 Hz), 3.68 (2H, s), 4.00 (2H, q, *J* = 7 Hz), 6.8~7.6 (6H, m). *Anal.* Found: C, 74.45; H, 8.51; N, 10.86. Calcd. for C₁₆H₂₂N₂O: C, 74.42; H, 8.53; N, 10.85%. KK-135: mp 90~91°C. NMR (CDCl₃) δ: 0.73 (9H, s), 3.80 (2H, s), 7.00 (1H, s), 7.1~7.5 (4H, m), 7.53 (1H, s). *Anal.* Found: C, 67.56; H, 6.86; N, 10.98. Calcd. for C₁₄H₁₇N₂Cl: C, 67.61; H, 6.84; N, 11.27%.