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Synthesis and Insect Growth Regulatory Activity of 1-Neopentyl-5-substituted Imidazoles

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A new series of 1-neopentyl-5-substituted imidazoles was synthesized and evaluated in silkworms, *Bombyx mori*, for activity inducing precocious metamorphosis. Most of the compounds induced precocious methamorphosis in the 4th instar larvae of *B. mori* by topical application (20μg/larva). 1-Neopentyl-5-phenylimidazole (1) showed relatively high activity. The introduction of a methoxy (KK-109) or an ethoxy (KK-110) substituent at the *ortho* position on the benzene ring increased the activity compared with that of compound 1, while the 4-alkoxyphenyl analogs showed decreased activity. The 4-chlorophenyl (KK-135) and 4-bromophenyl analogs also exhibited high activity. When the 3rd instar larvae were treated with a high dose of KK-110 or KK-135, a few larvae metamorphosed into precocious miniature pupae in the 3rd larval stage. The induction of precocious metamorphosis with KK-110 and KK-135 was inhibited by simultaneous application of methoprene, a juvenile hormone mimic.

INTRODUCTION

Recently we have reported that a large number of 1, 5-disubstituted imidazoles with a juvenile hormone (JH)-like terpene chain induced unequivocal precocious metamorphosis in silkworm, *Bombyx mori*, larvae, which was clearly recognized as a JH-deficiency symptom. 1-Citronellyl-5-phenylimidazole (KK-22) (Kuwano et ***al.,*** 1984) and 1-benzyl-5-[(*E*)-2,6-dimethyl-1, 7-heptadienyl] imidazole (KK-42) (Kuwano et al., 1985) have been found as two representative compounds showing marked activity. However, further investigations demonstrated that the JH-like terpene chain was not necessary for the activity ; 1-neopentyl-5-phenylimidazole showed an activity comparable to KK-22. In our previous short communication (Kuwano et al., 1988), we reported on the activity of several 1, 5-disubstituted imidazoles with a non-terpene chain. In this paper we describe details of the preparation and structure-activity relationships of 1-neopentyl-5-substituted imidazoles.

EXPERIMENTAL

Synthesis

All melting points were uncorrected. The NMR spectra were determined with a JEOL JNM-FX 100 spectrometer, using Me_4Si as an internal standard, and all samples were prepared in $CDCl_3$.

Compounds **1-7** (Table 1) were synthesized according to the procedure reported previously (Kikuchi ***et al.,*** 1990).

5-(3-Ethoxyphenyl)-1-neopentylimidazole (8)

A mixture of 1.3g of m-hydroxybenzaldehyde, lg of neopentylamine and 6g of anhydrous $MgSO_4$ in 30 ml of dichloromethane was refluxed for 2hr. $MgSO_4$ was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 ml of methanol, and to the mixture was added 6g of anhydrous K_2CO_3 and 2.5g of tosylmethylisocyanide (TosMIC). After refluxing for 2hr, the solvent was evaporated and water (70ml) was added to the residue. The precipitate was collected by filtration and recrystallized from ethanol and water to afford 0.8g (33 %) of 5-(3-hydroxyphenyl)-1-neopentylimidazole, mp 215~217°C.

To a suspension of 0.1g of sodium hydride (60 % in oil) in 10ml of dimethylformamide was added 0.46g of the above compound, and the mixture was stirred for 1hr at room temperature. To the mixture was added 0.22g of ethyl bromide at 0-5°C. After stirring for 20hr at room temperature, to the mixture was added 50ml of water, and the product was extracted with ether. The ether solution was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel by elution with hexane-ethyl acetate (2 : 1) and (1 : 1). Concentration of the hexane-ethyl acetate (1 : 1) eluate under reduced pressure followed by recrystallization of the residue from hexane afforded 0.35g (68 %) of 8, mp 67-68°C. NMR δ: 0.74 (9H, s), 1.42 (3H, t, J = 7Hz), 3.82 (2H, s), 4.02 (2H, q, J = 7Hz), 6.7-7.5 (6H, m). Anal. Found : C, 74.49 ; H, 8.56 ; N, 10.70. Calcd. for $C_{16}H_{22}N_2O$: C, 74.42 ; H, 8.53 ; N, 10.85 %.

5-(4-*Ethoxyphenyl*)-*1-neopentylimidazole (9)* was prepared in the same manner as 8, using p-hydroxybenzaldehyde. Yield 66 %. mp 70-72°C. NMR δ : 0.74 (9H, s), 1.44 (3H, t, J = 7Hz), 3.76 (2H, s), 4.05 (2H, q, J = 7Hz), 6.7-7.5 (6H, m). Anal. Found : C, 74.39 ; H, 8.60 ; N, 10.83. Calcd. for $C_{16}H_{22}N_2O$: C, 74.42 ; H, 8.53 ; N, 10.85 %.

Compounds 11-13 were similarly prepared, starting from compound 5 and the corresponding alkyl bromides.

1-Neopentyl-5-(2-propoxyphenyl) imidazole (11). Yield 81 %. NMR δ : 0.72 (9H, s), 0.90 (3H, t, J = 7Hz), 1.45-1.90 (2H, m), 3.66 (2H, s), 3.86 (2H, t, J = 7Hz), 6.7-7.5 (6H, m).

5-(2-Isopropoxyphenyl)-1-neopentylimidazole (12) Yield 28 %. NMR δ : 0.72 (9H, s), 1.20 (6H, d, J = 6Hz), 3.73 (2H, s), 4.2-4.6 (1H, m), 6.8-7.6 (6H, m).

5-(2-Isobutoxyphenyl)-1-neopentylimidazole (13) Yield 21 %. NMR δ : 0.72 (9H, s), 0.88 (6H, d, J = 6Hz), 1.7-2.1 (1H, m), 3.64 (2H, d, J = 6Hz), 3.66 (2H, s), 6.7-7.5 (6H, m).

5-(4-Methoxyphenyl)-1-neopentylimidazole (10). A mixture of 1.4g of *p*-methoxybenzaldehyde, 1.2g of neopentylamine, and 5g of anhydrous $MgSO_4$ in 30 ml of dichloromethane was refluxed for 2hr. $MgSO_4$ was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 ml of methanol, and to the mixture was added 5g of K_2CO_3 and 2.5g of tosylmethylisocyanide. After refluxing for 2hr, the solvent was evaporated and the product was extracted with ether. The ether solution was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel by elution with hexane-ethyl acetate (3 : 1) and (1 : 1). Concentration of the hexane-ethyl acetate (1 : 1) eluate under reduced pressure followed by recrystallization of the residue from hexane afforded 0.2g (41 %) of 10, mp 1022103°C. NMR δ : 0.73 (9H, s), 3.76 (2H, s), 3.82 (3H,

s), 6.7-7.5 (6H, m). Anal. Found: C, 73.77 ; H, 8.27 ; N, 11.39. Calcd. for $C_{15}H_{20}N_2O$: C, 73.77 ; H, 8.20 ; N, 11.48 %.

Compounds 14-23 were similarly prepared, starting from the appropriate substituted benzaldehyde and neopentylamine.

5-(2-methylphenyl)-1-neopentylimidazole (14). Yield 5.7 %. NMR δ : 0.76 (9H, s), 2.16 (3H, s), 3.57 (2H, s), 6.90 (1H, s), 7.0-7.3 (4H, m), *7.52* (1H, broad s).

5-(3-methylphenyl)-1-neopentylimidazole (15). Yield 4.4 %. mp 72-74°C. NMR δ : 0.73 (9H, s), 2.36 (3H, s), 3.84 (2H, s), 6.9-7.4 (5H, s), 7.94 (1H, broad s).

5-(4-methylphenyl)-1-neopentylimidazole **(16).** Yield 4.4 %. mp 98-99°C (recrystallized from hexane). NMR δ : 0.72 (9H, s), 2.37 (3H, s), 3.80 (2H, s), 6.95 (1H, broad s), 7.14-7.24 (4H, m), 7.46(1H, broad s). Anal. Found: C, 78.67 ; H, 8.74 ; N, 12.21. Calcd. for $C_{15}H_{20}N_2$: C, 78.95 ; H, 8.77; N, 12.28 %.

5-(4-Ethylphenyl)-1-neopentylimidazole (17). Yield 6.7 %. mp 45-47°C. NMR δ : 0.72 (9H, s), 1.26 (3H, t, J=7Hz), 2.66 (2H, q, J=7Hz), 3.80(2H, s), 6.94 (1H, broad s), 7.06-7.12 (4H, m), 7.46(1H, broad s).

5-(4-Bromophenyl)-1-neopentylimidazole (18). Yield 1.1 %. mp 127-130°C. NMR δ : 0.72 (9H, s), 3.78(2H, s), 6.9-7.6 (6H, m).

5-(3,4-Dichlorophenyl)-1-neopentylimidazole **(19).** Yield 0.7 %. mp 132-134°C. NMR δ : 0.74 (9H, s), 3.78(2H, s), 6.98 (1H, broad s), 7.10 (1H, dd, Ja=7Hz, Jb=2Hz), 7.36 (1H, d, J=2Hz), 7.44 (1H, d, J=7Hz), 7.50 (1H, broad s).

1-Neopentyl-5-(4-nitrophenyl) imidazole (20). Yield 1.0 %. mp 125-128°C. NMR 6 : 0.72 (9H, s), 3.84(2H, s), 7.08 (1H, broad s), 7.44 (2H, d, J=8Hz), 7.52 (1H, broad s), 8.22 (2H, d, J=8Hz).

5-(3,4-methylenedioxyphenyl)-1-neopentylimidazole (21). Yield 4.3 %. mp 123-125°C. NMR δ : 0.74 (9H, s), 3.74 (2H, s), 5.96 (2H, s), 6.64-6.96 (4H, m), 7.44 (1H, broad s).

5-(1-Naphthyl)-1-neopentylimidazole (22). Yield 2.9 %. NMR δ : 0.68 (9H, s), 7.07(1H, broad s), 7.24-7.92 (8H, m).

5-(2-Naphthyl)-1-neopentylimidazole (23). Yield 2.3 %. mp 128-130°C (recrystallized from hexane). NMR δ : 0.72 (9H, s), 3.88 (2H, s), 7.06 (1H, broad s), 7.28-7.90 (8H, m). Anal. Found : C, 81.70 ; H, 7.60 ; N, 10.54. Calcd. for $C_{18}H_{20}N_2$: C, 81.82 ; H, 7.58 ; N, 10.61 %.

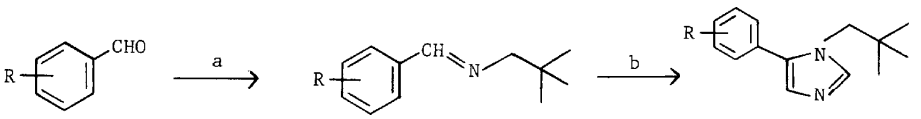
Bioassays

Bombyx mori (Gunpo x Shugyoku, C. 137 x N. 137) larvae were reared on artificial, diets, Silkmate 1S and 2M (Nippon Nosan Kogyo Co., Ltd) for 1st instar and the 2nd to 5th instar larvae, respectively, under a 12 hr light and 12 hr dark photoperiod at 26±2°C. The compounds in an acetone solution (1-4 μg/larva) were applied topically to newly molted 4th instar and 24 hr-old 3rd instar larvae of *B. mori*. The activity was evaluated by the induction of precocious metamorphosis : spinning a coccon and then pupation in the 3rd or 4th instar (penultimate) period. The lethal effect was defined as mortality within the same larval stage after treatment.

RESULTS AND DISCUSSIONS

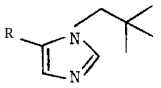
Syntheses

1-Neopentyl-5-substituted imidazoles were prepared according to procedures



Reagents ; (a) neopentylamine, $MgSO_4$, CH_2Cl_2 ; (b) TosMIC, K_2CO_3, MeOH,
Scheme 1. Synthesis of 1-neopentyl-5-substituted imidazoles

Table 1. Induction of precocious metamorphosis in the silkworm (Gunpo x Shugyoku) by 1 neopentyl — 5 -substituted imidazoles.



NO.	R	(μg/larva)	Precocious metamorphosis (%) 20	10	4	2
1	Phenyl		100	100	nt	0
2	2 — Chlorophenyl		30	0		
3	3 — Chlorophenyl		100	100	5	0
4	4 — Chlorophenyl		100	100	95	75
5	2 — Hydroxyphenyl		0			
6	2 — Methoxyphenyl		100	100	100	75
7	2 — Ethoxyphenyl		100	100	100	75
8	3 — Ethoxyphenyl		60	20	nt	0
9	4 -Ethoxyphenyl		70	80	0	
10	4 — Methoxyphenyl		0			
11	2 — Propoxyphenyl		100	100	85	nt
12	2 — Isopropoxyphenyl		nt	nt	90	10
13	2 — Isobutoxyphenyl		40	0		
14	2 — Methylphenyl		100	100	95	70
15	3-Methylphenyl		10	0		
16	4 — Methylphenyl		100	60	0	
17	4 — Ethylphenyl		100	30	0	
18	4 — Bromophenyl		100	100	75	45
19	3,4—Dichlorophenyl		0			
20	4 — Nitrophenyl		30	0		
21	3,4— Methylenedioxyphenyl		100	80	0	
22	**1** — Naphthyl		100	100	65	nt
23	2 — Naphthyl		0			

nt : not tested

described by van Leusen *et* al. (1977). The imines derived from neopentylamine and substituted benzaldehydes were treated with tosylmethylisocyanide (TosMIC) in the presence of potassium carbonate as a base in methanol to afford 1-neopentyl-5-substituted imidazoles (Scheme 1). In this method compounds **14**-**23** were prepared in low yield, whereas 5-(hydroxyphenyl)-1-neopentylimidazoles (e. g. compound 5) were obtained in relatively high yield because of presumably the stability of the imines derived from hydroxybenzaldehydes. Compounds 8-13 in Table 1 were prepared by standard alkylation of the corresponding 5-(hydroxyphenyl)-1-neopentylimidazoles.

Biological activities

The bioassay data for 1-neopentyl-5-substituted imidazoles on the 4th instar

larvae of *B. mori* are given in Table 1. As described in a previous paper (Kuwano et al., 1988), in a series of 1-substituted-5-pheylimidazoles the 1-neopentyl analog 1 showed the highest activity. So modifications were made in the 5-position of the imidazole ring by introducing various substituents on the benzene ring. The introduction of a 4-chloro substituent on the benzene ring (4) increased activity in comparison with that observed for the parent compound 1, whereas the 2-chlorophenyl analog 2 showed much less activity and the 3-chlorophenyl analog 3 was as active as 1. Interestingly, the 3, 4-dichlorophenyl analog 19 was quite inactive at 20 μg. The 2-hydroxyphenyl analog 5 had no activity at 20 μg, presumably due to the polarity of the hydroxy group.

The 2-methoxy-(6) and 2-ethoxyphenyl (7) analogs were more effective than unsubstituted 1. The location of an alkoxy group was important for activity. The 3- and 4-alkoxy analogs (S-10) decreased the activity compared with that of 1. The activity in the 22alkoxyphenyl analogs was found to fall off with increasing size of the alkyl chain (11-13). The 2-methylphenyl analog 14 exhibited high activity as well as compounds 6 and **7**. However, the introduction of an alkyl group at the *meta* or *para* position on the benzene ring decreased activity (**15-17**).

In contrast to 4-alkoxy-and 4-alkylphenyl analogs, the 4-bromophenyl analog 18 showed relatively high activity. The 4-nitrophenyl (20) and 3, 4-methylenedioxyphenyl (21) analogs showed low activity. The 1-naphthyl analog 22 had almost the same activity as that of compound 1, whereas the 2-naphthyl analog 23 did not induce precocious metamorphosis even at a dose of 20 μg.

In Table 2 there are presented the ED,, values for several representative 1, 5-disubstituted imidazoles showing high activity. The 2-methoxylphenyl analog 6 was the most active of the series of 1-neopentyl-5-substituted imidazoles and compounds 4, 7, 14 and 18 showed higher activity than KK-22 which has been reported to be highly active to the silkworm for the first time. However, 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 the silkworm.

The induction of precocious metamorphosis with compounds 4, 7 and 14 was inhibited by simultaneous application of methoprene, a JH mimic, as shown in Table 3. Those three compounds (10 μg/larva) induced precocious metamorphosis in 100 %

Table 2. Induction of precocious metamorphosis in the silkworm (C. 137 x N. 137) by 1,5-disubstituted imidazoles.

Compound	ED,, (μg/larva)
4 (KK-135)	2.1
6	1.1
7 (KK-110)	1.6
11	2.9
14	1.5
18	2.2
22	2.8
KK-22	2.8
KK-42	0.4

Table 3. Counteraction by methoprene on the effects of 1−neopentyl−5−substituted imidazoles for the 4th instar larvae.

Compound (10 μg/larva)	Precocious metamorphosis (%)	
	methoprene (μg/larva)	
	0	10
4 (KK-135)	100	0
7 (KK-110)	100	0
14	100	0

Table 4. Effects of compounds 4 (KK- 135) and 7 (KK-110) on the 3rd instar larvae of *B. mori*

Compound	dose (μg)	No. of dead larvae	No. of larvae which spun cocoons at 3rd	4th	5th (instar)
4 (KK-135)	1	0	0	1	19
	2	0	0	16	4
	5	0	0	20	0
	10	0	0	20	0
	20		0	19	0
	40	0	1	19	0
	60	0	1	19	0
	80	1	6	13	0
7 (KK-110)	1	0	0	4	16
	2	0	0	18	2
	5	0	0	20	0
	10	0	0	20	0
	20	3	0	17	0
	40	2	0	18	0
	60	6	4	10	0
	80	14	1	5	0
Control		0	0	0	20

No. of larvae tested= 20

of the 4th instarlarvae, while all of the larvae molted into normal 5th instar when 10 μg of methoprene was topically applied to those treated with compounds. This result indicated that 1-neopentyl-5-substituted imidazoles induced precocious metamorphosis by causing a JH-deficiency in the hemolymph of the silkworm larvae.

Table 4 shows the effects of two representative compounds 4 (KK-135) and 7 (KK-110) on the 3rd instar larvae (24 hr old larvae after the 2nd ecdysis). When the 3rd instar larvae were treated with low doses (1-20 μg) of both compounds, precocious pupation occurred in the 4th (penultimate) larval stage. At high doses of 60 and 80 μg some of larvae spun at the end of the 3rd instar larval stage and then metamorphosed into precocious miniature pupae, even though the percentage was low. In this case a few pupae molted to the miniature adults, but most of the pupae failed in adult

emergence.

KK-110 exhibited more toxicity than KK-135. The lethal effect occurred within the 3rd larval stage after treatment. It seems that this acute toxicity was not related to the JH-deficiency symptom, because concurrent application of methoprene did not rescue this mortality.

It has been reported that KK-42 inhibited ecdysteroid synthesis in the prothoracic glands of B. *mori* (Yamashita et *al.*, 1987) and *Locusta migratoria* (Roussel *et al.*, 1987) in vitro at a low dose. Recently Akai *et al.* (1989) have found that KK-42 depressed the JH amount in the hemolymph of B. *mori* larvae. Although the precise mode of action of KK-42 is still unknown, a new series of 1,5-disubstituted imidazoles might hold promise as insect growth regulators.

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