Original Article

Insecticidal Activities of Phenoxy Analogues of Dihydropipercide*

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In this series of communications, we have reported the isolation of an unsaturated amide, namely dihydropipercide [*N*-isobutyl-11-(3,4-methylenedioxyphenyl)-(2*E*, 4*E*)-2,4-undecadienamide] as well as two structurally related amides as insecticidal principles from fruits of *Piper nigrum* L. This communication describes the structure-insecticidal activity relationships of the phenoxy analogues of dihydropipercide. As a result, *N*-isobutyl-12-(3-Br, 3-Cl or 3-CF₃ phenoxy)-(2*E*, 4*E*)-2,4-dodecadienamides were selected as the most toxic compounds against *Callosobruchus chinensis* (adzuki bean weevil, about ten times as toxic as dihydropipercide). These selected amides revealed noticeable toxicities against *Chilo suppressalis* (rice stem borer), *Musca domestica* (housefly) and *Spodoptera litura* (tobacco cutworm). Electro-physiological study of the 3-CF₃ phenoxy derivative indicated that it acts on the central nerve cord as a neurotoxic principle. The amide caused *Periplaneta americana* (American cockroach) to knockdown by injection while the amide did not reveal knockdown effect when the same dosage was applied topically.

INTRODUCTION

In the preceding paper, we have described general synthetic methods and insecticidal activities of several amides structurally related to dihydropipercide **2** [*N*-isobutyl-11-(3,4-methylenedioxyphenyl)-(2*E*, 4*E*)-2,4-undecadienamide], a novel insecticidal principle from fruits of *Piper nigrum* L. As a result, *N*-isobutyl-12-(3,4-methylenedioxyphenoxy)-3-methyl-(2*E*, 4*E*)-2,4-dodecadienamide **3** was selected as a potent insecticidal compound (Fig. 1).¹⁾ In this paper, we describe detailed structure-insecticidal activity relationships of the phenoxy analogues of dihydropipercide

with various substituents on the aromatic ring and molecular size (chain length).

Pellitorine **1**, a representative of natural unsaturated *N*-isobutylamides, has been known as a paralyzing insecticidal agent as well as a pungent principle for the human, however its insecticidal mode of action has not been studied in detail until now. In the present paper some preliminary electro-physiological studies of dihydropipercide **2** as well as a selected unsaturated amide are also described.

MATERIALS AND METHODS

1. Materials

All products were fully characterized by ¹H NMR, IR and mass spectrometries as well as microanalyses where necessary.

1.1 *N*-isobutyl-12-(substituted phenoxy)-(2*E*, 4*E*)-2,4-dodecadienamides **10-18**

The synthesis of the amides containing 3,4-methylenedioxyphenoxy group has been re-

* The *Piperaceae* Amides (Part 7). For Part 6, see Ref. 1).

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Fig. 1

Fig. 2 General synthetic routes of unsaturated amides.

a) THP, *p*-TsOH. b) distillation. c) PCC oxid. d) NaOMe. e) KOH-MeOH, heat. f) $(\text{NPCl}_2)_3$, Et_3N , *i*-BuNH₂. g) dil. HCl. h) DCC.

ported in the preceding communication (see Ref. 1)) and the same synthetic route was employed in the present study (see Fig. 2).

1.2 Unsaturated amides with various chain length 19–23

As starting materials for the syntheses of amides **19**, **20**, **21**, **22** and **23**, 1,6-hexanediol, 1,7-heptanediol, 1,9-nonanediol, 1,10-decanediol and 1,12-dodecanediol were employed respectively, instead of 1,8-octanediol for **16**. The other synthetic routes were the same as described earlier.¹⁾

1.3 3-Methyl-2*E*,4*E*- and 3-methyl-2*Z*,4*E*-dienamide derivatives 24 and 25

Compounds **24** and **25** were synthesized by the same procedure described earlier.¹⁾

1.4 Reference insecticides

Pyrethrin I was obtained by TLC separation of natural pyrethrins. Purified DDT was obtained in this laboratory by chromatographic separation.

2. Methods

2.1 Measurements of insecticidal activities

Insecticidal activities of testing compounds against *Callosobruchus chinensis* (adzuki bean weevil), *Chilo suppressalis* (rice stem borer), *Musca domestica* (housefly) and *Spodoptera litura* (tobacco cutworm) were evaluated by the same procedures described in the preceding paper.¹⁾

2.2 Electro-physiological study on *Periplaneta americana* (American cockroach)

Adult male of *P. americana* were used in the experiments. Experimental details have been described in the preceding communication.²⁾

RESULTS AND DISCUSSION

In the preceding communication, we divided the key molecule (dihydropipericide, **2**) into three parts (parts A, B and C, Fig. 3) and the structure-activity relationships at each part revealed the structural requirements of part A (amine moiety) and part B (linear chain moiety) for insecticidal activity. Among the tested amides, compound **3** was selected as

Fig. 3 Dihydropipericide 2.

the most potent insecticidal principle. In this paper, our study was directed to the aromatic substituents of **3**. Table 1 lists the LD₅₀ values associated with various substituents on the benzene ring in *N*-isobutyl-12-phenoxy-(2*E*, 4*E*)-2,4-dodecadienamide. Activities of 3,4-methylenedioxy analogue **9**, natural pyrethrins and fenitrothion are also included in Table 1 for comparison. Compound **9** showed moderate toxicity, however introduction of a methyl, nitro or methoxy substituent at 4-position of the phenoxy group resulted in low activities (**10**, **11** and **12**). Halogen atom substituted derivatives at 4-position (**13** and **14**) were found to show high activities among the 4-substituted phenoxy analogues. 3-Halosubstituted analogues (**16** and **17**) displayed much

higher toxicities than their corresponding 4-substituted analogues.

As we expected, 3-trifluoromethyl analogue **18** and 3,4-dichloro analogue **15** also exhibited remarkable insecticidal effect. We should notice that the LD₅₀ values of **17** and **18** were smaller than that of fenitrothion.

The marked enhancement of toxicity by introduction of some functions at C₃ and/or C₄ might be attributed to a retardational effect of these substituents against oxidative metabolism, which is generally observed in the detoxification process for many classes of insecticides.³⁾

As a next step, insecticidal activities of 3-chlorophenoxy analogues of various chain length were investigated and the results are summarized in Table 2. The part B with 13 carbon atoms turned out to be optimum length for insecticidal activity (in this case, chain length were counted from the amide carbonyl carbon to the oxygen atom of phenoxy group; the ether oxygen was counted as a methylene).

On the other hand, 3-methyl-(2*E*, 4*E*)-2,4-dienamide **24** showed almost the same toxicity as that of the parent amide **16**. In the case of 3-chlorophenoxy series, introduction of 3-

Table 1 Insecticidal activities of *N*-isobutyl-12-(substituted phenoxy)-2*E*,4*E*-dodecadienamides to adult *C. chinensis* (male).

	Compounds	m.p. (°C)	LD ₅₀ (μg/insect) ^{a)}
9	X=3,4-methylenedioxy	140-141	2.00
10	4-CH ₃	96- 98	>10
11	4-NO ₂	101.5-103	8.00
12	4-OCH ₃	68- 71	>10
13	4-Cl	89.5- 92	0.15
14	4-Br	76- 77	0.25
15	3,4-diCl	74- 75	0.070
16	3-Cl	74- 78	0.068
17	3-Br	67- 71	0.038
18	3-CF ₃	75- 76	0.043
Pyrethrins	—	—	0.10
Fenitrothion	—	—	0.045

^{a)} Topical application (mortalities were evaluated after 24 hr).

Table 2 Insecticidal activities of 3-chlorophenoxy analogues of various chain lengths to adult *C. chinensis* (male).

	Compounds	m.p. (°C)	LD ₅₀ (μg/insect) ^{a)}
19		100–103.5	9.00
20		74–75	0.080
16		74–78	0.068
21		67–68	0.20
22		—	0.28
23		82–83	>10
24		n_D 1.5400 (20.5°C)	0.060
25		n_D 1.5441 (20.5°C)	10

^{a)} see Table 1.

methyl group did not result in a favourable effect. However, in the case of 3,4-methylenedioxyphenoxy series (see Table 3 in our preceding communication¹⁾), the 3-methyl analogue showed noticeable toxicity. 3-Methyl-(2*Z*, 4*E*)-analogue **25** showed no activity.

From both of the observations described above and the preceding communication,¹⁾ it may be concluded that all parts of the molecule (parts A, B and C) have their optimum structural features as follows:

Part A: Only isobutylamine and its structurally related saturated secondary amine analogues are acceptable. Steric limitation is fairly strict.

Part B: Optimum carbon chain length is C₁₃. Terminal benzyl group (Ph-CH₂-) can be replaced to phenoxy group (Ph-O-). (2*E*, 4*E*)-Dienamide moiety is essential. 3-Methyl substituent on the dienamide moiety is ac-

ceptable.

Part C: 3,4-Methylenedioxyphenyl group is not essential. 3-Halogen or 4-halogen substituent show good result. Especially, 3-halo-analogue as well as 3-trifluoromethyl analogue exhibit the highest toxicity.

The insecticidal activities of representative synthetic amides against several species of insects were investigated (see Table 3). Compound **16** showed only poor results against *M. domestica*, however the other three amides **2**, **17** and **18** exhibited complete kill at 500 ppm. Compound **2** showed no toxicity against *C. suppressalis*. Compounds **2** and **16** showed considerable toxicities against *S. litura*, on the other hand, neither of the two amides **17** and **18** revealed activity. In general, the order of insecticidal toxicities against *C. chinensis* were not necessarily consistent with those against the other insect species. From these

Table 3 Insecticidal activities of some representative amides against several species of insects.

Compounds	Activity (kill %) ^{a)}		
	Cs ^{b)}	Md ^{c)}	SI ^{d)}
2 ^{e)}	0	100	73
16	100	32	94
17	100	100	0
18	85	100	0

^{a)} Experimental methods are given in preceding communication.¹⁾

^{b)} *Chilo suppressalis*.

^{c)} *Musca domestica*.

^{d)} *Spodoptera litura*.

^{e)} LD₅₀ on *C. chinensis* was 0.23 µg/insect (see Ref. 1)).

observations, it will be still difficult to deduce any definite conclusion on their structure-insecticidal spectra relationships.

Although pellitorine **1**, has long been known as an insecticide, its mode of action has not been studied in detail until now. The three amides, pellitorine **1**, dihydropiperidine **2** and the selected amide **18** have a common structure unit [*N*-isobutyl-(2*E*, 4*E*)-2,4-dienamide moiety] and these three amides exhibited noticeable paralyzing action on several kinds

of insects. However, the insecticidal toxicities of the former was far inferior to those of the latter two amides **2** and **18**. Now, we describe the electro-physiological study of dihydropiperidine **2** and the selected amide **18** on the nervous system of *P. americana* (adult male), in comparison with those of pyrethrin I and DDT (see Table 4). The present two amides induced only repetitive discharge on the central nerve cord, but pyrethrin I induced conduction blockage as well as repetitive discharge.²⁾ On the other hand, DDT revealed no symptom on the central nerve cord within 30 min. From these observations, synthetic amides **2** and **18** seem to act on the nervous system.²⁾ This would have some relationship with the results that **2**, **18** and pellitorine **1** caused knockdown by injection (10 µg/insect), while these compounds did not reveal knock-down effect when the same dosage was applied topically.⁴⁾

Recent considerable success in the studies on synthetic pyrethroids⁵⁾ and juvenile hormone mimics⁶⁾ have resulted in the development of several thousand-fold or more active compounds as compared with their natural lead compounds, pyrethrins and juvenile hormone I, II and III. The present study has been the first successful modification of natural pepper amides which resulted in about 10 to 170 times increase of insecticidal activity

Table 4 Required time to induce each symptom on the central nerve cord of *Periplaneta americana* at 10⁻⁵ M treatment.

Compounds	Symptom (min)		
	IS ^{a)}	RD ^{b)}	CB ^{c)}
2	4.0	5.0	>30
18	3.0	3.5	>30
Pyrethrin I	0.3	0.3-1.0	15
DDT	>30	>30	>30

^{a)} Increase of number of spikes. ^{b)} Repetitive discharge: both spontaneous and stimulative firings were observed. ^{c)} Conduction blockage: this was determined by cessation of spontaneous activity and lack of response to a stimulus.

compared to those of dihydropipericide and pellitorine, respectively.

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要 約

ジヒドロペパーサイドのフェノキシ類縁体の殺虫活性*

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胡椒から得られたジヒドロペパーサイド [*N*-イソブチル-11-(3,4-メチレンジオキシフェニル)-(2*E*,4*E*)-2,4-ウンデカジエンアミド] を母核とし, そのフェノキシ類縁体の構造活性相関の研究を行なった。その結果, アズキゾウムシに対する活性の優れた化合物として, *N*-イソブチル-12-(3-ブロム, または 3-クロル, または 3-CF₃フェノキシ)-(2*E*,4*E*)-2,4-ドデカジエンアミドが選択された。これらアミド類のニカメイチュウ, イエバエおよびハスモンヨトウに対する殺虫活性も調べた。また, ゴキブリの神経を用いた電気生理の研究より, これら一連の胡椒アミド類は神経に作用する化合物であることが判明した。

* 胡椒アミドの研究 (第7報)