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Chemical Synthesis and Toxicity of α-Cyano-3- Phenoxy Benzyl-1-(2, 2-Dimethyl-2-Hydroxy Ethyl)-1-Isopropyl-P-Chlorophenyl Acetate as a New Compound of Synthetic Pyrethroids

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ABSTRACT

The α-isopropyl position (valeric acid moiety) of sumicidin reacts readily with acetone in the presence of base medium to give α-cyano-3-phenoxybenzyl-1-(2,2-dimethyi-2-hydroxyl ethyl)-1-isopropyl-p-chlorophenyl acetate (sumicidin ethyl derivative). The yield product of the new adduct was 96.7%. The spectroscopic analysis using Nuclear Magnetic Resonance (N.M.R), Infrared (I.R) and Gas chromatography / Mass Spectrometry (GC/MS) was applied to confirm the chemical structure. The N.M.R. spectra for the new product (sumicidin ethyl derivative) established the loss of proton from α-isopropyl carbon (acid moiety) at 5.25 ppm, addition of two methyl groups from acetone at 1.40 and 1.65 ppm and proton from the hydroxyl group introduced at 0.6 ppm. The I.R spectra showed the presence of "CH $(CH_3)_2$" group at 1360-1380 cm^{-1} (two bands) and "COH" group at 1060 cm^{-1}. The GC/MS, spectra confirmed the spectral data of N.M.R. and I.R. However the ethyl derivative of sumicidin gave a single peak at t_R =9.11 min., while the parent compound gave a single peak at t_R= 5.19 min and the mass spectral fragments, suggests that derivatization occurs at the α-isopropyl position of the acid moiety. The comparative toxicity of sumicidin as well as its ethyl derivative was evaluated against the 4^{th} instars of *culex pipiens* as a medical pest. The ethyl derivative of sumicidin showed higher toxicity than its corresponding parent compound by 4 fold against the mosquito larvae.

Key Words: Synthetic Pyrethroids; Sumicidin; Sumicidin ethyl derivative; Spectroscopy; Toxicity

INTRODUCTION

The synthetic pyrethroids were introduced to the field of pesticides during 1950's and since this decade, drastic change have been occurred in the synthesis of this type of insecticides. (Corral & Elliott 1965; Elliott *et al*., 1971, Ohano *et al*., 1976; Itaya *et al*., 1977; Elliott *et al*., 1981; Bosone *et al*., 1986; Michael *et al*., 1988; Kazunori *et al*., 1989).

The chemical structure of the major synthetic pyrethroids are esters of α-cyano-3-phenoxybenzyl alcohol with either chrysanthemic acid e.g., cypermethrin and deltamethrin (Aketa *et al*., 1978) or with valeric acid e.g., flucythrinate and sumicidin (Kondo *et al*., 1977). The synthesis of 3-phenoxybenzyl chrysanthemates and their dihalovinyl analogs substituted with cyano group was described by several authors (Katsuda, 1974; 1975; Elliott *et al*., 1978; lantzsch *et al*., 1980; Kurary, 1981). Other chrysanthemate pyrethroids have also been prepared and tested as medical insecticides (Wilson & Mound, 1974; Mulla *et al*., 1978; Ralph & Westby, 1980; Roberts, 1982; Helson & Surgeoner, 1986; Holck & Meek, 1987; Marzouk *et al*., 1995). α-cyanophenoxybenzyl pyrethroids reacts with pentafluorobenzyl bromide at the benzilic position to give pentafluorobenzyl derivatives to enhance analytical ECD-detection (Saleh *et al*., 1980) and reacts with acetone at benzilic position (Marzouk, 1990), vinyl position (Marzouk *et al*., 1995) or α-isopropyl position (Marzouk, 1996) to give acetone derivatives to enhance the insecticidal toxicity.

The aim of the present study is to synthesize a new compound of synthetic pyrethroids more toxic to the medical pests and low pollutant to the environment.

MATERIALS AND METHODS

Tested pyrethroids. Sumicidin (97%) technical grade, α-cyano-3-phenoxybenzyl-α-isporopyl-p-chlorophenylacet- -ate was obtained from Sumitomo Chemical Company, Japan while sumicidin ethyl derivative was prepared according to the method as described by Marzouk (1996).

Chemical synthesis of sumicidin ethyl derivative

I. Chemical reaction. The reaction of sumicidin with acetone is applied in the present investigation. However, acetone solution of (0.2mM) of sumicidin was refluxed for 48 hrs in the presence of suspension of Na_2CO_3 (base medium). The product was isolated by filtration, evaporated to dryness, dissolved in ether, washed with water and then saturated with NaCl, dried over anhydrous Mg SO_4 and solvent evaporated.

II. Identification tests. The chemical structure of the synthesized compound was obtained using spectroscopic analysis of:

a) Nuclear Magnetic Resonance (^{1}H.N.M.R) spectroscopy. Spectroscopic data for the derivative of sumicidin, as well as its parent compound (sumicidin) were confirmed using proton nuclear magnetic resonance "Varian EM-390" spectrometer, with tetramethyl silane (TMS) as internal standard and deutero chloroform as solvent. The N.M.R spectra of synthetic pyrethroids and related

compounds were scanned (Janes, 1977; Syrier, 1980; Marzouk *et al*., 1995; Marzouk, 1996).

b) Infrared (I.R) Spectroscopy. Nicolet FT Raman spectrometer using Nujal mull was used to collect the data on infrared (IR) spectroscopy.. The I.R spectra of α-cyano pyrethroids and their derivatives were illustrated by the method of Marei *et al*. (1988).

c) GC/MS Spectroscopy. For gas chromatography (GC) coupled with mass spectrometry (MS), spectroscopic analysis was run using the Finnigan mat SSQ7000 spectrometer with fused silica glass capillary column(0.25 mm i.d.30m), helium as the carrier gas (40 cm/s) and electron-capture detector (ECD). The temperature conditions were as follows; 320°C, 300°C and 380°C for the injector, column and detector respectively. For mass spectral fragments, all data were for the electron impact mode. Relative intensities were based on the most intense ion as 100% (molecular ion). The GC/MS technique of synthetic pyrethroids and other pesticides was described according to Saleh *et al.* (1980) and Katritzky *et al.* (1995).

lll. Toxicity of Sumicidin and its ethyl derivative. Laboratory insect strain of mosquito larvae, *Culex pipiens* was used for testing the toxicity of sumicidin ethyl derivative and its parent compound. The stock colony of the susceptible strain was obtained from High Institute of Public Health, Alexandria University. The culture of insects was fed on 60-80 meshes powder mixture of equal parts of biscuits, dried yeast and dried unfatty milk in laboratory hygrothermic conditions of 20-25°C and 65-70% R.H. All the experiments were carried out using the 4^{th} instars of *Culex pipiens*. Each treatment was replicated thrice. The percent mortality was recorded 24 hours after exposure. Three glass cups contained 99 mL of tap water and 1 mL of absolute acetone were considered as control. The percent mortalities resulting from the three replicates for each concentration were fitted by eye. The concentration required to kill 50% of the larvae (LC_{50}) was determined directly from the concentration mortality regression line in term of part per million (ppm).

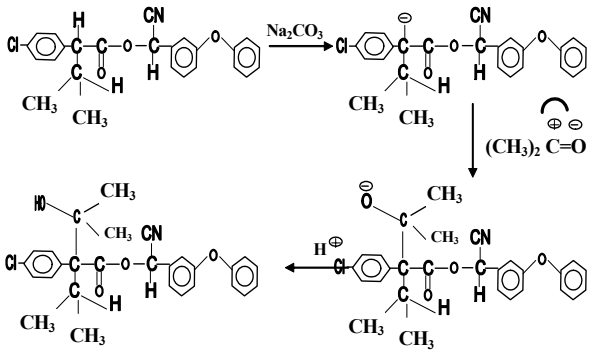
The LC_{50} values, slopes and confidence limits were calculated by the probit analysis (Finney, 1971). In all experiments, percent mortality was corrected by Abbott's formula (1925).

RESULTS AND DISCUSSION

Synthesis of α-cyano-3-phenoxybenzy-1-(2, 2-dimethyl-2-hydroxy ethyl)-1-isopropyl-p-chlorophenyl acetate

I. Chemical Synthesis. The benzylic position of α-cyano-3-phenoxy benzyl pyrethroids reacts readily with acetone to form-2-(3-phenoxybenzoyl -2- propyl esters (Saleh *et al*,1980) to achieve new derivatives more sensitive for ECD-GLC. 2-(3-phenoxybenzoyl-2-propyl easter.) derivatives of deltamethrin and fenpropathrin were synthetized (Marzouk 1990) to evaluate it as new insecticidies. Since the present study is a continuation in part of this type of work, the ethyl derivative of sumicidin was prepared (Fig. 1) in a similar manner as described above. The yield percentage of isolated derivative is 96.7%.

Fig. 1. Suggested chemical derivatization of α-cyano-3-phenoxybenzyl-1-(2,2-dimethyl-2-hydroxy ethyl) -1-isopropyl-p-chlorophenyl acetate (Sumicidin ethyl derivative)



II. Spectroscopic Analysis

1. Nuclear Magnetic Resonance (^{1}H.N.M.R). The nuclear magnetic resonance was run using a Varin, EM-390 spectrometer to confirm the structure of sumicidin ethyl derivative as well as its parent compound. Spectroscopic data obtained for N.M.R spectra are in agreement with results of Marzouk *et al.* (1995) for cypermethrin compound and Marzouk (1996) for flucythrinate compound (Table I).

However, N.M.R spectra of the present work shows the loss of proton from α-isopropyl position (valeric acid) at 5.25 ppm, additional of two methyl groups ($2CH_3$) from acetone at 1.40 and 1.65 ppm and also hydroxyl group (OH) are introduced at 0.6 ppm (Fig. 1). The results differed from those of Saleh *et al.* (1980) who reported that the derivatizaion of α-cyano pyrethroids with acetone occurs on the alcohol moiety.

2. Infrared (I.R) Spectroscopy. Infrared spectra were recorded for sumicidin ethyl derivative. The results obtained in the present study are in agreement with those reported by Marzouk *et al*. (1995) and Marzouk (1996). However, I.R spectra showed that the acetone molecule is substituted at the acid moiety (valeric acid) to give sumicidin ethyl derivative (Table II).

The I.R spectra indicates the presence of CH $(CH_3)_2$ group at 1360-1380 cm^1 (two bands) and (COH) group at 1060 cm^{-1} (Fig. 1).

3. GC/MS Spectroscopy. To confirm the structure of sumicidin ethyl derivative the GC/MS was run. The data in Table III represents, different retention time between sumicidin (single peak at t_R =5.19 min) and its ethyl derivative (single peak at t_R = 9.11 min).

Moreover, the fragmentation patterns confirmed that the new ethyl derivative is formed, i.e., m/e of the molecular ion was 477.5. The fragmentation scheme illustrated in Fig. 2 suggests that the derivatization occurred at the α-isopropyl

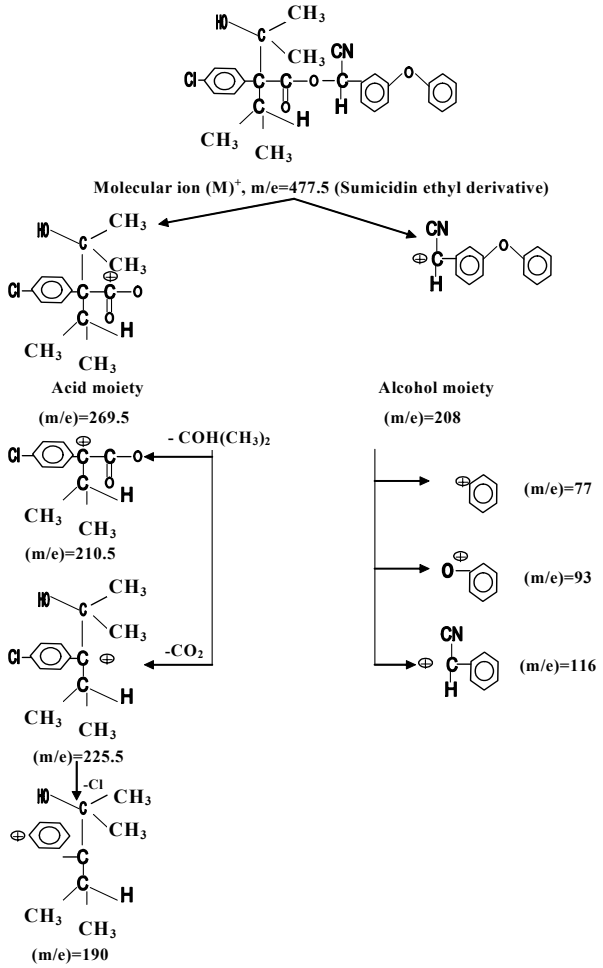
Table I. Nuclear Magnetic Resonance (^{1}H.N.M.R) chemical shifts (ppm) of sumicidin and its ethyl derivative comparing with previous studies

Synthetic Pyrethroides	Cypermethrin Marzouk *et al* (1995)	Cypermethrin ethyl derivative Marzouk *et al* (1995)	Flucythrinate Marzouk (1996)	Flucythrinak ethyl derivative Marzouk (1996)	Sumicidin Present work	Sumicidin ethyl derivative Present work
Substitution on	Acid moiety (chrysanthemic)	Acid moiety (chrysanthemic)	Acid moiety (valeric)	Acid moiety (valeric)	Acid moiety (valeric)	Acid moiety (valeric)
Substituents:	Chemical shifts (ppm)					
CH_3	1.2,1.3	0.8,0.9,1.2,1.3	0.85,0.95	0.85,0.95,1.35,1.60	0.87,0.98	0.87,0.98,1.40,1.65
COH	------	0.5	------	0.6	------	0.6
$CH(CH_3)_2$	------	------	5.20	------	5.25	----------
C= CH	5.35	------	------	------	------	-------

Table II. Infrared (I.R) bands of sumicidin and its ethyl derivative comparing with previous studies

Synthetic Pyrethroides	Cypermethrin Marzouk *et al* (1995)	Cypermethrin ethyl derivative Marzouk *et al* (1995)	Flucythrinate Marzouk (1996)	Flucythrinak ethyl derivative Marzouk (1996)	Sumicidin Present work	Sumicidin ethyl derivative Present work
Substitution on	Acid moiety (chrysanthemic)	Acid moiety (chrysanthemic)	Acid moiety (valeric)	Acid moiety (valeric)	Acid moiety (valeric)	Acid moiety (valeric)
Functional group (bonds)	Wave number (cm^{-1})					
COH	--------	1060	---------	1050	-------	1060
$CH(CH_3)_2$	-------	1360-1380	---------	1360-1380	-------	1360-1380

Fig. 2. Mass spectrum scheme (fragmentation patterns) of sumicidin ethyl derivative.



proton of isopropyl position (CH-CH $(CH_3)_2$) is absent and (COH-$(CH_3)_2$) from acetone is introduced.

The obtained results of these study lead to the conclusion that the chemical product of the present reaction is α-cyano-3-phenoxybenzyl-1- (2,2-dimethyl-2-hydroxy ethyl) -1-isopropyl-p-chlorophenyl acetate.

III. Toxicity Test of sumicidin and its ethyl derivative. The toxicity of sumicidin ethyl derivative was compared with sumicidin against the 4th instars of *culex pipens* using dip method (Marzouk, 1990). The results including LC_{50} values, confidence limits, slopes and toxicity index were obtained and the data are presented in Table IV. The data showed a clear difference between the slope values of sumicidin ethyl derivative (slope= 7.153) and sumicidin (slope= 4.832). These results may be explained in view of difference of mode of action and physicochemical properties of these compounds (Atamanalp *et al.*, 2002; Benli, 2005; Righi & Palermo-Neto, 2005). It is interest to indicate that the ethyl derivative of sumicidin is more toxic

Table III. Retention time (t_R) of sumicidin and its ethyl derivative on an fused silica capillary column of GC

Retention time (t_R), min		
Synthetic pyrethriod	parent compound	Ethyl derivative
Sumicidin	5.19	9.11

Table IV. Comparative toxicity of sumicidin and sumicidin ethyl derivative to the 4th istar larvae of *Culex pipiens* after 24 hrs of treatment

Synthetic pyrethroids	LC_{50} (ppm)	LC_{50} (Confidence limits)	Slope	Toxicity Index*
Sumicidin	0.0058	0.0049-0.0067	4.832	25.8
Sumicidin ethyl derivative	0.0015	0.0012-0.0017	7.153	100

*Toxicity Index = $\frac{LC_{50} \text{ of the most toxic compound}}{LC_{50} \text{ of the less toxic compound}} \times 100$

(LC_{50}=0.0015 ppm) than sumicidin (LC_{50}=0.0058 ppm) by 4 fold approximately.

Similar results have been reported by Marzouk *et al.* (1995), that the ethyl derivative of cypermethrin was more toxic than cypermethrin against the 4^{th} instars of *Culex pipiens* by 17 fold.

CONCLUSIONS

Generally, the data in the present study lead the conclusion that the new product obtained from the reaction of sumicidin and the acetone molecule may be considered as an alternative to be used against, *Culex pipiens* as medical pest with low environmental pollution.

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