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Insecticidal Activity of Cyanohydrin and Monoterpenoid Compounds

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Abstract: The insecticidal activities of several cyanohydrins, cyanohydrin esters and monoterpenoid esters (including three monoterpenoid esters of a cyanohydrin) were evaluated. Topical toxicity to *Musca domestica* L. adults was examined, and testing of many compounds at 100 μg/fly resulted in 100% mortality. Topical LD_{50} values of four compounds for *M. domestica* were calculated. Testing of many of the reported compounds to brine shrimp (*Artemia franciscana* Kellog) resulted in 100% mortality at 10 ppm, and two compounds caused 100% mortality at 1 ppm. Aquatic LC_{50} values were calculated for five compounds for larvae of the yellow fever mosquito (*Aedes aegypti* (L.)). Monoterpenoid esters were among the most toxic compounds tested in topical and aquatic bioassays.

Keywords: Cyanohydrin, monoterpenoid, insecticide.

Introduction

There is a growing need for effective, biodegradable pest-control compounds. Nineteen new major pesticides were introduced from 1961 to 1970, eight from 1971 to 1980, and only three from 1981 to 1985 [1]. Several recent publications from our laboratory have reported insect activity in cyanohydrin [2] and monoterpenoid compounds [3–5]. Naturally occurring cyanohydrins from flax, cassava, bam-

boo, peach pits and almonds probably serve a chemical defense function in the plants to protect against insect herbivory [6]. Hundreds of monoterpenoids are produced in plant essential oils, and apparently serve a defensive function as well [7]. In the current work we report the synthesis and biological activities of several new simple cyanohydrins, as well as novel cyanohydrin esters and monoterpenoid esters. Three compounds were monoterpenoid esters of a potent synthetic cyanohydrin, 1-cyano-1-hydroxy-2-propene (**1**; synonyms: CHP, 2-hydroxy-3-butenenitrile, acrolein cyanohydrin). CHP is an analog of two naturally occurring cyanohydrins in flax. These three cyanohydrins, CHP, methyl ethyl ketone cyanohydrin and dimethyl ketone cyanohydrin, have been shown to be potent insect fumigants [2]. We examined the activity in topical application to adult house flies (*Musca domestica* L.), as well as in aquatic bioassay to brine shrimp (*Artemia franciscana* Kellog) and the larvae of the yellow fever mosquito (*Aedes aegypti* (L.)).

Results and Discussion

The cyanohydrins synthesized by the methods reported in this study and tested against the invertebrates are shown in Figure 1.

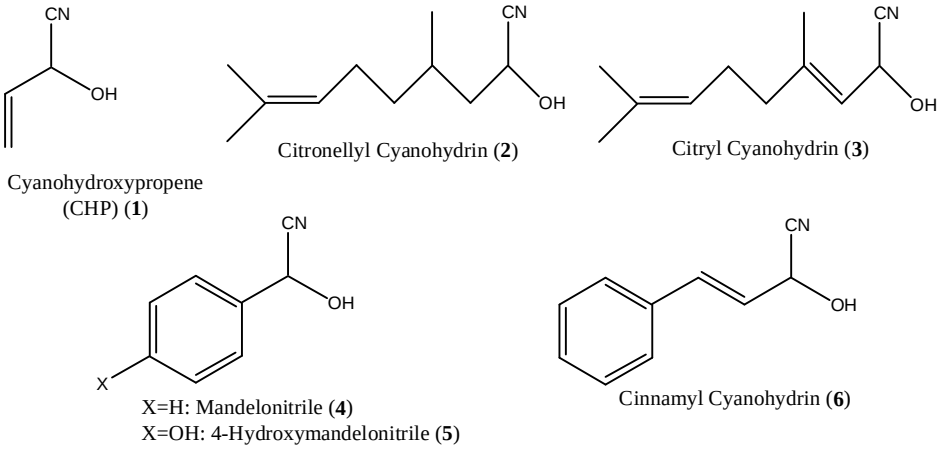


Figure 1. Structures of cyanohydrin compounds tested in this study.

Figure 2 shows the structures of cyanohydrin esters synthesized by the reported methods. Note that compounds **12**, **13** and **15** are monoterpenoid esters of the cyanohydrin CHP (**1**).

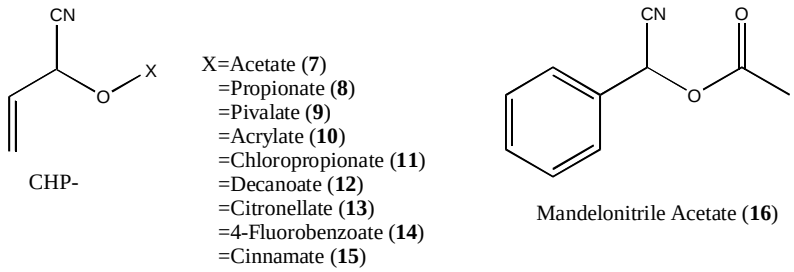
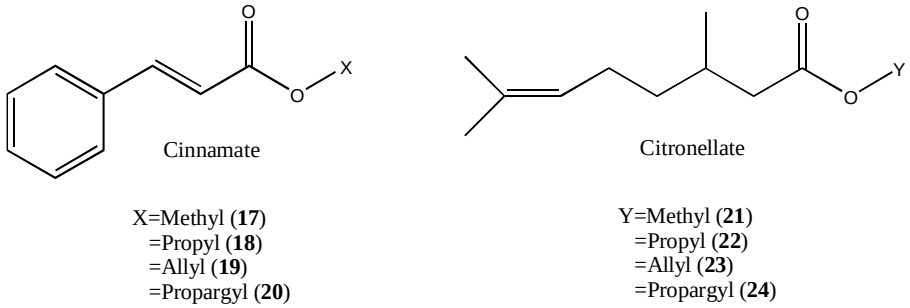


Figure 2. Structures of cyanohydrin esters.

Figure 3 shows the structures of esters of two monoterpenoids, cinnamic acid and cironellic acid.



X=Methyl (**17**)
=Propyl (**18**)
=Allyl (**19**)
=Propargyl (**20**)

Y=Methyl (**21**)
=Propyl (**22**)
=Allyl (**23**)
=Propargyl (**24**)

Figure 3. Monoterpenoid esters.

Topical testing on *M. domestica* showed that most of the cyanohydrins and their analogs had LD_{50} values between 10 and 100 μg/fly (Table 1). Monoterpenoid esters containing the alcoholic moieties CHP (**12**, **13** and **15**), propargyl (**20** and **24**) and allyl (**19** and **23**), all three of which are unsaturated, were the most effective. The presence of the CHP moiety was not always associated with high toxicity, and esterification of CHP with acetate, propionate or pivalate moieties produced less effective compounds than esterification of CHP with monoterpenoid moieties (compare **7**–**9** to **12**, **13** and **15** in Table 1). More studies need to be conducted in order to determine the nature of toxicity in relation to structure.

Table 1. Results of topical toxicity testing on *M. domestica* (percentage mortality).

N°	Compound	100 μg/fly	10 μg/fly	1 μg/fly
1	CHP	100	0	5
7	CHP acetate	100	0	0
8	CHP propionate	100	0	0
9	CHP pivalate	80	0	0
12	CHP decanoate	100	64	0
13	CHP citronellate	100	91	0
15	CHP cinnamate	87	50	0
17	Methyl cinnamate	50	0	10
18	Propyl cinnamate	38	0	0
19	Allyl cinnamate	100	40	4
20	Propargyl cinnamate	100	35	0
21	Methyl citronellate	57	5	4
22	Propyl citronellate	41	0	0
23	Allyl citronellate	100	17	5
24	Propargyl citronellate	100	15	0
	Control (acetone blank)	0		

The three cyanohydrin-monoterpenoid esters were among the most toxic compounds tested, with CHP citronellate (**13**) being the most toxic, showing 91% mortality at 10 μg/fly. CHP decanoate (**12**), CHP cinnamate (**15**), allyl cinnamate (**19**) and propargyl cinnamate (**20**) showed appreciable mortality at 10 μg/fly as well. Topical LD_{50} values on *M. domestica* (95% fiducial limit) were calculated by using SAS [8] and are reported in Table 2.

Table 2. Topical LD_{50} values to *Musca domestica* (expressed in μg/fly) and 95% fiducial limits.

N°	Compound	LD_{50}	95% FL
2	Citronellyl cyanohydrin	> 50	
3	Citryl cyanohydrin	> 50	
4	Mandelonitrile	7.06	5.45, 8.54
5	4-Hydroxy mandelonitrile	33.1	25.5, 47.5
6	Cinnamyl cyanohydrin	12.7	10.2, 15.7
16	Mandelonitrile acetate	14.5	11.8, 17.8

Aquatic testing with *A. franciscana* resulted in 100% mortality at 100 ppm for nearly all compounds tested (Table 3).

Table 3. Results of acute (24-hr) toxicity testing on *Artemia franciscana* (percentage mortality).

N°	Compound	100 ppm	10 ppm	1 ppm
1	CHP	100	63	20
3	Citryl cyanohydrin	87	0	0
6	Cinnamyl cyanohydrin	100	15	25
7	CHP acetate	0	0	0
9	CHP pivalate	100	30	23
10	CHP acrylate	100	43	30
11	CHP chloropropionate	100	43	33
12	CHP decanoate	100	95	15
13	CHP citronellate	100	100	40
14	CHP 4-fluorobenzoate	20	27	13
15	CHP cinnamate	100	100	95
17	Methyl cinnamate	100	80	35
18	Propyl cinnamate	100	100	65
19	Allyl cinnamate	100	100	95
20	Propargyl cinnamate	100	100	90
21	Methyl citronellate	100	100	45
22	Propyl citronellate	100	100	100
23	Allyl citronellate	100	100	100
24	Propargyl citronellate	100	64	25
	Control	4		

Several compounds showed 100% mortality at 10 ppm, and two compounds, propyl citronellate (**22**) and allyl citronellate (**23**), displayed 100% mortality at 1 ppm. The most toxic compounds tested on *A. franciscana* were esters of cinnamic acid or citronellic acid. Esterification of CHP with monoterpenoid moieties produced more effective compounds than esterification with the smaller moieties (compare **12**, **13** and **15** to **7** and **9**–**11** in Table 3). The cyanohydrins and cyanohydrin esters were of lower toxicity than monoterpenoid esters (**17**–**24**), except for CHP citronellate (**13**) and CHP cinnamate (**15**).

Aquatic LC_{50} values (95% fiducial limit) for *A. aegypti* larvae were calculated by using SAS [8] and are reported in Table 4.

Table 4. LD_{50} values (expressed in ppm) to *Aedes aegypti* larvae and 95% fiducial limits.

N°	Compound	LC_{50}	95% FL
1	CHP	2.75	1.94, 3.80
9	CHP pivalate	8.22	4.59, 17.8
10	CHP acrylate	5.19	3.55, 7.72
11	CHP chloropropionate	14.0	9.68, 23.9
14	CHP 4-fluorobenzoate	3.77	1.78, 7.78

For all tests, it appeared that esterification of CHP (**1**) with a nonmonoterpenoid moiety resulted in equal or lower activity in relation to CHP itself, and this was possibly related to moiety size and polarity. This result was also seen in the comparison of mandelonitrile (**4**) to mandelonitrile acetate (**16**) in topical LD_{50} values for *M. domestica.* Esterification of CHP with a monoterpenoid moiety, however, resulted in equal or higher activity in relation to CHP in topical and aquatic testing. Only three CHP-monoterpenoid esters were tested in this study; therefore, any conclusions regarding comparative effectiveness due to the properties of the monoterpenoid moieties are speculative. It is possible that their hydrolysis *in vivo* results in two insecticidal moieties, CHP and a monoterpenoid acid.

The limited series presented here indicates that alcoholic moieties containing double or triple bonds may be more effective than saturated ones, as methyl and propyl monoterpenoid esters were less effective than CHP, allyl or propargyl esters. Monoterpenoid esters were in most cases more toxic than monoterpenoid cyanohydrins. Esterification of some monoterpenoids has been demonstrated previously to enhance insecticidal activity [4,5].

Experimental

The structures of compounds **1**–**6** are shown in Figure 1, and the numerical designations used in this paper are as follows: 1-cyano-1-hydroxy-2-propene (CHP) (**1**), citronellyl cyanohydrin (i. e., the cyanohydrin synthesized from citronellal) (**2**), citryl cyanohydrin (**3**), mandelonitrile (**4**), 4-hydroxymandelonitrile (**5**) and cinnamyl cyanohydrin (**6**).

Structures of cyanohydrin esters are shown in Figure 2, and are named as follows: CHP acetate (**7**), CHP propionate (**8**), CHP pivalate (**9**), CHP acrylate (**10**), CHP 3-chloropropionate (**11**), CHP decanoate (**12**), CHP citronellate (**13**), CHP 4-fluorobenzoate (**14**), CHP cinnamate (**15**) and mandelonitrile acetate (**16**).

Monoterpenoid esters tested are shown in Figure 3: methyl cinnamate (**17**), propyl cinnamate (**18**), allyl cinnamate (**19**), propargyl cinnamate (**20**), methyl citronellate (**21**), propyl citronellate (**22**), allyl citronellate (**23**) and propargyl citronellate (**24**).

Compounds **1**–**3** and **6** were synthesized from potassium cyanide and their corresponding aldehyde. Stoichiometric amounts of potassium cyanide, the reactant aldehyde and glacial acetic acid were required. Potassium cyanide (KCN) was added to anhydrous diethyl ether and stirred with a magnetic stir bar. The aldehyde corresponding to the desired cyanohydrin was added slowly to the reaction mixture. Glacial acetic acid was added, and the reaction proceeded until the reactant aldehyde was no longer detected by thin-layer chromatography. The ethereal reaction mixture was washed three times with a saturated aqueous $NaHCO_3$ solution, and the aqueous portion was back-extracted with three volumes of diethyl ether and the water layer discarded. The diethyl ether was removed by rotary evaporation, and the product purified by using column chromotography as necessary. Compounds **4** and **5** were purchased from Sigma Chemical (St. Louis, MO, USA).

Cyanohydrin esters **8**–**11**, **14** and **16** were synthesized from their corresponding cyanohydrins and acid chlorides, following the method of Rice and Coats [4]. A method more suitable for synthesizing esters from cyanohydrins and carboxylic acids, utilizing dimethylaminopyridine (DMAP) and dicyclohexylcarboxiimide (DCC), was used for esters **12**–**13** and **15** [5]. This method was also used for the synthesis of monoterpenoid esters **17**–**24**. Compound **7** (also known as 2-acetoxy butenenitrile) was purchased from Aldrich Chemical (Milwaukee, WI, USA).

Topical bioassays to *M. domestica* (Orlando regular strain) were conducted after Rice and Coats [4] using a 1-µl volume of acetone to deliver the chemical to the thoracic venters of house flies. The mosquito larvae (*A. aegypti*) and brine shrimp (*A. franciscana*) were tested by adding the chemical to water according to the method of Tsao *et al.* [9]. The mosquito larvae were provided by Dr. W. A. Rowley, Medical Entomology Laboratory at Iowa State University, Ames, IA. The brine shrimp were purchased from Carolina Biological Supply (Burlington, NC).

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Samples Availability: Available from the authors.