CYCLOALKYL AND CYCLOARYL ESTERS OF HYDROXYBENZENEACETIC ACID AS REPELLENTS OF ADULT *TRIBOLIUM CONFUSUM*[1] IN THE LABORATORY[2]

W. R. Halliday,[3] T. P. McGovern,[4] and L. L. McDonald[3,5]
Stored-Product Insects Research and Development Laboratory
Agricultural Research Service, U. S. Department of Agriculture
Savannah, GA 31403
(Accepted for publication August 11, 1986)

ABSTRACT

Twenty-two cycloalkane and two aryl esters of mandelic acid (α-hydroxybenzeneacetic acid) were tested for repellency against adult confused flour beetles, *Tribolium confusum* Jacquelin du Val. High levels of repellency were found only with the cycloalkane esters. Among these esters, repellency increased as size of the ring increased to the cyclooctyl analog. When the cycloalkyl moiety also contained a straight-chain alkyl group, repellency generally increased over that of the parent cycloalkyl ester. When the alkyl group contained branching at the 1-position, the level of repellency was markedly below that of their straight-chain isomers. The 2-cyclohexylethyl and 3-cyclohexylpropyl mandelates were the most effective repellents in this study with average repellencies of 83.8 and 82.6%, respectively.

Key Words: *Tribolium confusum,* esters, hydroxybenzeneacetic acid, repellents.

J. Entomol. Sci. 21(4): 322-328 (October 1986)

INTRODUCTION

Preventing infestation of packaging materials by stored product insects would be a major accomplishment in the battle against these pests. Infestation can be minimized by treating the exterior packaging with materials which are toxic or cause repellency (Highland et al. 1984). In an ongoing project at the Stored-Product Insects Research and Development Laboratory, materials are continually tested for repellent activity against adults of the confused flour beetle, *Tribolium confusum* Jacquelin du Val. Various esters of mandelic acid (α-hydroxybenzeneacetic acid) exhibit strong repellent activity against these insects (McGovern et al. 1977, 1984; Gillenwater et al. 1981). Saturated mandelic acid ester compounds were generally better repellents than their unsaturated analogs (McGovern et al. 1984). Among alkynyl mandelates with alcohol chain lengths greater than 3 carbons the length of the chain did not greatly influence repellency (Gillenwater et al. 1981). However, the position of the triple bond did; the closer it was to the ester linkage, the higher the repellency. This paper summarizes the results of tests with 22 cycloalkane and cycloalkene derivatives and 2 aryl derivatives of mandelic acid. A

[1] Coleoptera: Tenebrionidae.
[2] Mention of a chemical does not constitute an endorsement or recommendation for its use by the U. S. Dept. of Agriculture nor does it imply registration under FIFRA as amended.
[3] Stored-Product Insects Research and Development Laboratory, Savannah, GA 31403.
[4] Insect Chemical Ecology Laboratory, Agricultural Environmental Quality Institute, Beltsville, MD 20705.
[5] Retired.

structure-activity relationship is proposed between the observed repellency and the chemical structures.

MATERIALS AND METHODS

The esters of mandelic acid were synthesized at the Insect Chemical Ecology Laboratory in Beltsville, MD, and purified by conventional methods. Purity was > 95% as determined by gas chromatography.

The procedures of Gillenwater and McDonald (1975) were followed. In this assay 10 unsexed adults, were placed in each of 4 circular open glass arenas centered on kraft paper bonded to alumninum foil. The kraft paper was treated with 25, 100, or 200 $\mu g/cm^2$ of the ester and joined lengthwise to an untreated piece of kraft paper. The insects thus had a choice of remaining on the treated or untreated sides. The repellency classification used the following scale:

$$\% \text{ Repellency} = \left[1 - \frac{(\#\text{ of insects on treated side})}{(\#\text{ of Readings})\ (20)}\right] 100. \qquad \text{Equation 1}$$

Class	Mean % Repellency
0	-0.1 to 0.1
I	0.1 to 20.0
II	20.1 to 40.0
III	40.1 to 60.0
IV	60.1 to 80.0
V	80.1 to 100.0

A standard mixture of pyrethrins + piperonyl butoxide with each group of materials applied at the rate of 5 + 50 $\mu g/cm^2$ produced a mean percent repellency (R) of 53.0. All testing and aging of treated papers were done at 27 ± 1°C and 60 ± 5% RH.

RESULTS

Repellencies of the compounds are listed in Table 1. Since there was generally a dose-dependent response to the repellents, only the highest dosage (200 $\mu g/cm^2$) will be discussed in detail. In this assay, compounds considered promising must be Class III or greater. Fourteen of the twenty compounds can thus be considered promising (Nos. 2, 3, 4, 6, 7, 8, 9, 11, 12, 18, 19, 21, 22, and 23).

There are four subgroups of compounds. Compounds 1 - 5 comprise cycloalkane esters of increasing ring sizes. Compounds 7 - 10 include cyclohexyl derivatives of increasing alkyl chain length. Compounds 12 - 15 are derivatives of secondary alcohols. Compounds 7, 18, 19, 21-23 fall into the final grouping and are derivatives of the cyclohexylmethyl ester of increasing size. Compounds not listed in these subgroups do not easily fall into any category and they are treated individually.

The effect of increasing ring size is shown by comparing compounds 1 - 5. In this series repellent activity peaked at 70.6% with the cyclooctyl ester. Lower activity was found with larger or smaller molecular weight compounds.

Table 1. Repellency of cyclic cycloalkane esters of mandelic acid to adult *Tribolium confusum*.

No.	Mandelate	Application rate ($\mu g/cm^2$)	% repellency after 1 wk	2 wk	4 wk	8 wk	AVG % repellency	Class*
1	Cyclopentyl	25	15.0	2.5	2.5	-11.3	2.2	I
		100	11.3	-2.5	-3.8	12.5	4.4	I
		200	61.3	43.8	2.5	-2.5	26.3	II
2	Cyclohexyl	25	15.0	23.6	6.6	4.6	12.5	I
		100	56.0	34.0	4.6	-1.4	23.3	II
		200	77.6	47.6	37.0	32.6	48.7	III
3	Cycloheptyl	25	16.6	22.6	10.6	32.6	20.6	II
		100	38.0	68.6	39.6	44.6	47.7	III
		200	51.6	76.0	57.0	56.0	60.2	IV
4	Cyclooctyl	25	45.6	19.0	8.6	32.6	26.5	II
		100	75.0	55.0	61.0	39.6	57.7	III
		200	78.6	66.0	82.6	55.0	70.6	IV
5	Cyclododecyl	25	24.0	-25.0	2.0	6.0	1.8	I
		100	13.0	0.0	2.0	14.0	7.3	I
		200	37.6	6.0	17.0	9.6	17.6	I
6	2-Methylcyclohexyl	25	8.8	10.0	6.3	-12.3	3.2	I
		100	50.0	28.8	-3.8	-26.3	12.2	I
		200	80.0	73.8	22.5	6.3	45.7	III
7	Cyclohexylmethyl	25	63.0	27.6	-16.4	28.0	25.6	II
		100	83.6	77.6	19.6	32.0	53.2	III
		200	92.0	92.0	36.6	59.0	69.9	IV
8	2-Cyclohexylethyl	25	52.6	24.6	15.0	22.6	28.7	II
		100	83.0	84.6	82.6	63.0	78.3	IV
		200	83.0	83.0	90.0	79.0	83.8	V
9	3-Cyclohexylpropyl	25	7.0	9.6	-26.4	15.6	1.5	I
		100	73.0	70.0	59.6	27.0	57.4	III
		200	84.6	85.6	88.0	72.0	82.6	V

Table 1. Continued.

No.	Mandelate	Application rate ($\mu g/cm^2$)	% repellency after 1 wk	2 wk	4 wk	8 wk	AVG % repellency	Class*
10	4-Cyclohexylbutyl	25	5.0	10.6	-7.6	0.6	2.2	I
		100	30.0	30.0	25.6	6.6	23.1	II
		200	31.6	38.0	45.0	35.0	37.4	II
11	3-Cyclopentylpropyl	25	71.3	77.5	28.8	-5.0	43.2	III
		100	81.3	93.4	48.8	38.8	65.6	IV
		200	71.3	86.3	72.5	71.3	75.4	IV
12	1-Cyclohexylethyl	25	22.6	7.6	-3.0	-2.6	6.2	I
		100	61.6	57.6	10.0	47.0	44.1	III
		200	78.6	77.0	17.0	53.0	56.4	III
13	1-Cylohexylpropyl	25	14.0	-1.4	-0.6	-4.0	2.0	I
		100	-9.4	10.6	27.0	13.0	10.3	I
		200	41.0	57.0	21.0	34.0	38.3	II
14	1-Cyclohexylbutyl	25	5.0	3.6	-14.4	9.6	1.0	I
		100	-33.0	-16.4	6.0	-16.6	-15.0	IA
		200	-26.0	-7.0	11.6	-15.0	-9.1	IA
15	1-Cyclohexylpentyl	25	19.0	3.0	7.6	0.0	7.4	I
		100	0.0	3.6	32.0	23.0	14.7	I
		200	-4.4	0.0	47.6	20.0	15.8	I
16	Benzyl	25	5.0	14.6	-5.0	15.6	7.6	I
		100	17.0	9.0	20.6	29.0	18.9	I
		200	8.0	14.6	16.6	40.0	19.8	I
17	3-Phenylpropyl	25	-7.4	-6.4	13.8	3.0	0.8	I
		100	32.0	36.6	20.6	25.0	28.6	II
		200	46.6	41.0	25.0	23.0	33.9	II
18	Cycloheptylmethyl	25	55.6	9.0	-1.6	26.0	22.3	II
		100	83.6	41.0	31.6	27.6	46.0	III
		200	90.0	64.6	57.6	35.6	62.0	IV

Table 1. Continued.

No.	Mandelate	Application rate ($\mu g/cm^2$)	% repellency after 1 wk	2 wk	4 wk	8 wk	AVG % repellency	Class*
19	Cyclooctylmethyl	25	23.0	8.6	-3.0	-8.6	5.0	I
		100	66.0	40.6	16.6	37.6	40.2	III
		200	75.0	73.6	37.0	50.6	59.1	III
20	4-(1,1-Dimethylpropyl) cyclohexyl	25	11.6	6.0	0.0	38.6	14.1	I
		100	4.6	-9.4	17.6	15.6	7.1	I
		200	4.0	-10.4	-8.0	69.6	13.8	I
21	3-Cyclohexenylmethyl	25	36.6	7.6	-15.6	-2.0	6.7	I
		100	73.0	65.0	55.0	54.6	61.9	IV
		200	69.6	61.0	59.0	65.0	63.7	IV
22	2-Norbornanylmethyl	25	65.6	49.0	13.6	26.0	38.6	II
		100	70.0	63.6	60.0	74.0	66.7	IV
		200	68.6	64.0	63.0	77.0	68.2	IV
23	cis-Myrtanyl	25	39.6	27.0	19.0	53.0	34.7	II
		100	67.0	73.0	28.0	33.6	50.4	III
		200	54.0	69.0	12.0	48.0	45.8	III
24	Cyclopropylmethyl	25	30.0	-11.3	7.5	-17.5	2.2	I
		100	52.5	40.0	-22.5	-17.5	13.2	I
		200	71.3	60.0	-8.8	-6.3	28.1	II

* Values with an A indicate attractancy.

Addition of a methyl group at the 2 position to the cyclohexyl ester compound (No. 2), did not drastically alter repellency. Introduction of an alkyl straight-chain between the cyclohexyl and carboxyl groups resulted in a progressive increase in repellency as chain length increased to 3 methylene units (Compounds 7 to 9). There was a sharp loss of repellent activity when the chain length was increased to include a fourth methylene unit (No. 10). High repellent activity was maintained when the six membered ring of this series (No. 9) was replaced with a cyclic pentane group (No. 11) (75.4% R). This group of esters contains the 2 most effective repellents in the study: the 2-cyclohexylethyl and 3-cyclohexylpropyl mandelates had average repellencies of 83.8 and 82.6%, respectively.

The importance of the primary alcohol moiety in the alkyl chains was emphasized by the minimal repellency shown by compounds 12 to 15 which are branched isomers of compounds 7 to 10. Only No. 12 showed activity comparable to the pyrethrins/PB standard (Class III). Similar results were observed with alkynyl mandelates (Gillenwater et al. 1981) and with branched-chain mandelates (McGovern et al. 1984) when branching occurred in the 1-position.

The effect on repellency of substituting aromatic rings for the cyclohexyl ring was investigated by testing the aryl analogs of No. 7, cyclohexylmethyl mandelate, and 13, cyclohexylpropyl mandelate. The benzyl analog (No. 16) showed little repellency (19.8% R) while the phenylpropyl analog (No. 17) had weak (Class II) repellency.

Comparing No.'s 7, 18, 19, and 24 shows a slight trend toward decreased repellency as the ring size varied from the cyclohexylmethyl standard. However, when the repellency of these compounds are compared to their parent ring compounds (No.'s 2, 3, and 4) varying results were obtained. No. 7 (cyclohexylmethyl) showed increased repellency over No. 2 (cyclohexyl); compounds 3 (cycloheptyl) and 18 (cycloheptylmethyl) were about equivalent, and No. 19 (cyclooctylmethyl) was inferior to No. 4 (cyclooctyl). When a 1,1-dimethylpropyl group was added para to the ester linkage (No. 20) no activity could be detected. Addition of a 3,4-double bond to the cyclohexylmethyl parent compound (No. 7) had little effect on repellency (No. 21). Compounds 22 and 23 are bicyclo esters which both contain a methylene bridge. Compound 22 had the same level of activity, on the average, as both the parent compound (No. 7) and compound 18, which also has a 7 carbon atom alicyclic ring moiety. Its greater persistence, however, can be noted when the 8 week readings are compared. The repellency at 8 weeks was comparable with that of compound 8, which is also a derivative of an 8 carbon alcohol. *cis*-Myrtanyl mandelate (No. 23) was less repellent than either No. 7 or 22. However, *cis*-myrtranyl mandelate is a larger molecule than either 7 or 22 and is equivalent to No. 10 as a derivative of a primary 10 carbon alcohol. No. 23 showed superior repellency to No. 10, especially at the lower dosages and in overall persistence. The most effective esters in each subgrouping were derivatives of a 7 or 8 carbon alcohol, i.e., compound 4 (in series No. 1 to 5), compound 8 (in series No. 7 to 10) No. 12 (in series No. 12 to 15), and No.'s 21 and 22 (No. 7, 18, 19, 21, 22, and 23).

DISCUSSION

Results presented here establish a structure-activity relationship of certain cycloalkane and cycloalkene derivatives of mandelic acid. Activity decreased when

branching at the 1-position of the alcohol moiety occurred, when the cyclohexane ring was replaced by an aromatic ring, and when the carbon chain length between the ester linkage and the ring exceeded 3 carbons. The latter observation is opposite to the finding of Gillenwater et al. (1981) who found there was no appreciable decrease in repellency as chain length increased. There was also no decrease in the repellency of long chain saturated mandelates once the minimum of 6 carbons was reached (McGovern et al. 1977). Compounds tested in this series of cycloaryl and cycloalkyl mandelates were not as repellent as 3,7 dimethyloctyl mandelate which to date has been the most effective mandelate tested (McGovern et al. 1984).

LITERATURE CITED

Gillenwater, H. B., and L. L. McDonald. 1975. Repellency of nineteen candidate compounds to adult *Tribolium confusum.* J. Ga. Entomol. Soc. 10: 151-55.

Gillenwater, H. B., T. P. McGovern, and L. L. McDonald. 1981. Repellents for adult *Tribolium confusum:* Alkynyl mandelates. J. Ga. Entomol. Soc. 16: 106-12.

Highland, H. A., A. H. Kamel, M. M. El-Sayed, E. Z. Fam, R. Simonaitis, and L. D. Cline. 1984. Evaluation of permethrin as an insect-resistant treatment on paper bags and of tricalcium phosphate as a suppressant of stored product insects. J. Econ. Entomol. 77: 240-46.

McGovern, T. P., H. B. Gillenwater, and L. L. McDonald. 1977. Repellents for adult *Tribolium confusum:* Mandelates. J. Ga. Entomol. Soc. 12: 79-84.

McGovern, T. P., J. L. Zettler, and L. L. McDonald. 1984. Repellents for adult *Tribolium confusum:* Mandelic acid esters of branched-chain alcohols. J. Ga. Entomol. Soc. 19: 356-66.