A New Class of Pyrethroidal Insecticides; α-Substituted Phenylacetic Acid Esters

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Continuing studies on structure modification of the naturally occurring insecticide pyrethrin have disclosed a variety of synthetic pyrethroid. Progress in the modification of the alcohol moiety as ester of chrysanthemic acid were most remarkable. In fact, all examples of the industrially available pyrethroids such as allethrin (Ia),[1a] tetramethrin (Ib),[1b] resmethrin (Ic)[1c] and phenothrin (Id)[1d]* are esters of chrysanthemic acid. The modification of the acid moiety also resulted in discoveries of a series of cyclopropanecarboxylic acids such as (IIa), (IIb) and (IIc).[2a,2b,2c]

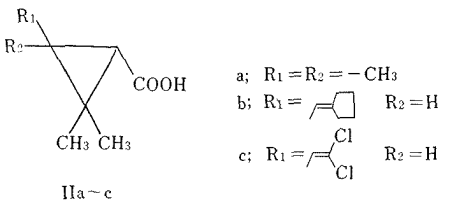
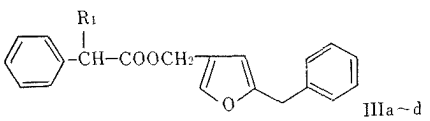


FIG. 1.

However, all the attempts to prepare any of insecticidally active acid moieties without cyclopropanecarboxylic acid group were entirely fruitless.[3] So, it was commonly believed that the cyclopropanecarboxylate moiety is essential for being insecticidally active.

We now wish to report a new class of substitituted phenylacetic acid esters whose insecticidal potencies are fairly competitive and of similar nature to those of the conventional pyrethroids. The new insecticidal esters are shown by the substituted phenylacetate (III), (IV) and (V) in which R_1 and R_2 can be a variety of functional groups and particular examples with toxicities to *Musca domestica* (strain: Lab-em-7-em) are described in Tables (I), (II) and (III).

TABLE I.

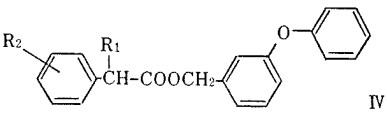


	R_1	n_D (°C)	LC_{50} (mg/100 ml)[a]	Relative toxicities
IIIa	CH_3–	1.5571 (22.5)	>> 2000	< 7.5
IIIb	CH_3CH_2–	1.5545 (17.0)	260	58
IIIc	$(CH_3)_2CH$–	1.5443 (24.0)	150	100
IIId	$(CH_3)_2CHCH_2$–	1.5356 (22.0)	>> 2000	< 7.5

[a] By Campbell's turn table method (*Soap and Sanit. Chem.*, **14**, 119 (1938))

* Ia to Id are corresponding *d,l-(trans, cis)*-chrysanthemates of the following alcohols, (Ia); *d,l*-allethrolone, (Ib); N-hydroxymethyl-3,4,5,6-tetrahydrophthalimide, (Ic); 5-benzyl-3-furylmethanol, (Id); 3-phenoxybenzyl alcohol.

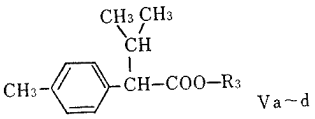
TABLE II.



IVa~e

	R_1	R_2	n_D (°C)	LC_{50} (mg/100ml)[a]	Relative toxicities
IVa	$(CH_3)_2CH-$	4-Cl-	1.5655 (21.5)	83	375
IVb	CH_3CH_2-	4-Br-	1.5861 (17.0)	197	158
IVc	$CH_2=C(CH_3)-$	3-Cl-	1.5845 (24.5)	108	288
IVd	$(CH_3)_2CH-$	4-CH_3O-	1.5640 (17.0)	65	478
IVe	$(CH_3)_2CH-$	3,4-CH_2O_2	1.5731 (21.5)	49	635
	Phenothrin			38	818
	Pyrethrin			311	100

TABLE III.

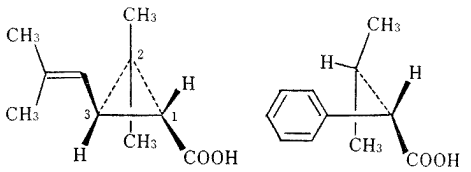


Va~d

	R_3	n_D (°C)	LC_{50} (mg/100ml)	Relative toxicities
Va	5-Benzyl-3-furylmethyl	1.5433 (25.0)	42	100
Vb	3-Phenoxybenzyl	1.5596 (28.5)	72	58
Vc	5-Propargyl-2-furylmethyl	1.5215 (26.0)	500	8.4
Vd	Allethronyl	1.5274 (21.0)	560	7.5

The phenylacetates whose α-substituents are isopropyl, isopropenyl or *tert*-butyl[4] groups are highly toxic, while the α-ethyl analogs are moderately toxic. It is of interest that the α-methyl, α-*n*-propyl, α-*n*-butyl or higher analogs are non-toxic as well as the non-substituted analogs.[5] Marked enhancements in toxicities are observed when appropriate functions such as methyl, methoxy, chloro or bromo groups are introduced to the *para* or *meta* position of the phenyl group of the acid moiety. In contrast, introduction of the substituents at the *ortho* position causes on available data decrease in toxicities.[5] Table II compiles a number of particular examples of the esters of 3-phenoxybenzyl alcohol whose toxicities to house flies are several times higher than that of pyrethrin and fairly competitive with that of the corresponding ester of chrysanthemic acid or

phenothrin. Table III shows a series of α-isopropyl-4-methylphenylacetic acid esters whose alcohol moieties are well-known as ester of chrysanthemic acid, the conventional pyrethroids. The ester of (+)-S-α-ethylphenylacetic acid is nearly twice toxic relative to that of the racemic ester, and all the available examples[6] allow a generalization that the (S)-α-modifications are far more toxic than the enantiomerics. These structural requirements for the substituted phenylacetic acid esters as potent insecticide appear to be similar with those for chrysanthemic acid esters when compared with the absolute structures in Fig. 2.



(1R,3R)-Chrysanthemic acid (S)-α-Isopropylphenylacetic acid

FIG. 2.

This is the first report of potent synthetic pyrethroids without cyclopropanecarboxylate functions.

Preparation of the phenylacetates

Most of the phenylacetic acids were prepared from corresponding phenylacetonitriles by known methods, which were converted into acid chlorides ($SOCl_2$), and esterified with appropriate alcohols.

The isopropenyl phenylacetate (IVc) was synthesized from 3-chlorophenylacetic acid as follows, i) condensation with acetone in the presence of two equivalents of *i*-PrMgBr, ii) esterification with 3-phenoxybenzyl bromide in DMF with NEt_3, iii) dehydration with P_2O_5 in refluxing benzene.

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4) Y. Okuno and T. Umemura, unpublished results.
5) Y. Okuno and N. Ohno, unpublished results.
6) M. Miyakado, N. Ohno and Y. Okuno, unpublished results which will be reported elsewhere.