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Syntheses of Diastereoisomers of the Recent Pyrethroids, Fenvalerate (S-5602) and Cypermethrin (NRDC-149) from (−)-3-Phenoxy-mandelic Acid and Determination of Their Absolute Configurations

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A variety of the recent Pyrethroids containing α-cyano-3-phenoxybenzyl alcohol moiety, *i.e.*, Fenvalerate (S-5602), Cypermethrin (NRDC-149), and Decamethrin (NRDC-161) *etc.* are under extensive development for agricultural pests control in many countries.[1]

Concerning Fenvalerate Miyakado *et al.* indicated that the acid moiety of the insecticidally more active ester had S configuration.[2] It is also known that the acid moiety of the more active isomers of Cypermethrin have either 1R,3S (*d-trans*) or 1R,3R (*d-cis*) configuration. But the absolute configurations of the α-cyanobenzyl alcohol moiety of the two pyrethroids remained undetermined in connection with insecticidal activity.

We first describe isolation and bioassay of individual optical isomers from diastereoisomer mixture of Fenvalerate and Cypermethrin whose absolute configurations of the acid moieties are S (to Fenvalerate) and 1R,3S (to Cypermethrin) respectively.

A diastereoisomer mixture of Fenvalerate or (R S)-α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-isovalerate, which was prepared by esterification with α-bromo-3-phenoxyphenylacetonitrile and sodium (S)-2-(4-chlorophenyl)-isovalerate, could be separated by SiO_2 column chromatography (eluent: hexane–AcOEt (40: 1)) into two diastereoisomers. The late eluting diastereiosiomer, Fenvalerate α (crystal mp 57~58°C) was far more toxic to insects than the early eluting one, Fenvalerate β (liquid).

The diastereoisomer pair of Cypermethrin were similarly isolated from (R S)-3-phenoxybenzyl (1R, 3S)-2, 2-dimethyl-3-(2, 2-dichrolovinyl)-cyclopropane-carboxylate or *d-trans* Cypermethrin by the similar column chromatography and the late eluting diastereoisomer, *d-trans* Cypermethrin α was also far more toxic than the early eluting one or *d-trans* Cypermethrin β. Insecticidal activities of the respective isomers of Fenvalerate and Cypermethrin are compiled in Table I.

TABLE I. INSECTICIDAL ACTIVITIES OF FENVALERATE α,β AND *d-trans* CYPERMETHRIN α,β

Compound	Insecticidal activities to houseflies[a] LD_{50}γ/fly	Relative toxicities
Fenvalerate α[b]	0.008	100
Fenvalerate β[c]	0.4	2.0
d-trans Cypermethrin α[d]	0.003	100
d-trans Cypermethrin β[d]	0.072	4.2

[a] *Musca domestica* strain WHO (by topical application).

[b] NMR $\delta_{TMS}^{CDCl_3}$: 0.68 (d, 3H, J=7.0 Hz), 0.93 (d, 3H, J=7.0 Hz), 6.32 (s, 1H), $[\alpha]_D^{21}$ −11.2° (c=6.5, $CHCl_3$).

[c] $\delta_{TMS}^{CDCl_3}$: 0.72 (d, 3H, J=7.0 Hz), 1.05 (d, 3H, J=7.0 Hz), 6.30 (s, 1H), $[\alpha]_D^{21}$ −12.3° (c=2.2, $CHCl_3$). It contains 0.3% Fenvalerate α by GLC analysis.

[d] NMR $\delta_{TMS}^{CDCl_3}$: 1.16 (s, 3H), 1.22 (s, 3H), 5.62 (d, 1H, J=8.0 Hz), 6.38 (s, 1H), $[\alpha]_D^{24}$ −5.6° (c=0.87, $CHCl_3$).

[e] NMR $\delta_{TMS}^{CDCl_3}$: 1.18 (s, 3H), 1.30 (s, 3H), 5.57 (d, 1H, J=8.0 Hz), 6.36 (s, 1H), $[\alpha]_D^{24}$ −16.4° (c= 0.70, $CHCl_3$). It contains 4.4% *d-trans* Cypermethrin α by GLC analysis.

We further report determination of the absolute configurations of the alcohol moiety of the two pyrethroids by synthetic correlation to a Decamethrin[3] isomer in the following enantio- and diastereoselective synthetic pathways.

(±)-3-Phenoxy-mandelic acid could be first resolved with D-(−)-threo-1-*p*-nitrophenyl-2-amino-1,3-propanediol yielding the (−)enantimer in 95% optical purity.*1 In order to determine the absolute configuration, the (−) isomer was esterified with (1R,3R)-2,2-dimethyl-3-(2,2-dibromovinyl)-cyclopropanecarboxylic acid chloride (2a) and pyridine to afford the O-acylated (−)-3-phenoxy-mandelic acid (3a). Anhydrous sodium salt of the carboxylic acid was converted to the acid amide (4a) after chlorination with oxalyl chloride followed by treatment with anhydrous ammonia. The acid amide (4a) was finally dehydrated with P_2O_5 in boiling benzene to give the cyanohydrin ester (5a) (see Fig. 1). The cyanohydrin ester (5a) was identical in all respects (IR, NMR, TLC and GLC) with known (R)-α-cyano-3-phenoxybenzyl (1R,3R)-2, 2-dimethyl-3- (2, 2-dibromovinyl) -cyclopropane-carboxylate*2 which is diastereomeric to Decamethrin. Therefore R configuration could be defined to (−)-3-phenoxy-mandelic acid.*3

Then a diastereoisomer of Fenvalerate, (R)-α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-isovalerate (5b) was similarly prepared from (S)-2-(4-chlorophenyl)-isovaleric acid chloride (2b) and (−)-3-phenoxy-mandelic acid (1) and was identical in the all respects with the insecticidally less active Fenvalerate *β*. Therefore the absolute configuration of the α-cyanobenzyl carbon atom in Fenvalerate *β* is R, accordingly Fenvalerate α (the most active diastereoisomer) must have a S configuration at the α-cyanobenzyl carbon atom.

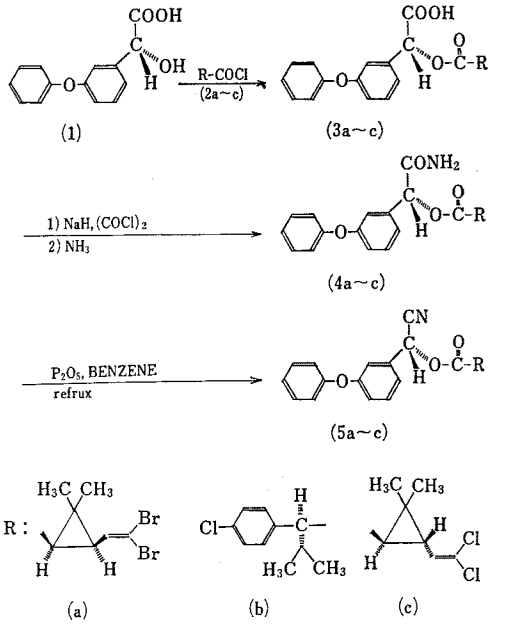

FIG. 1. Synthetic Pathways of Optically Active Cyanohydrin Esters.

Similarly a diastereoisomer of Cypermethrin, (R)-α-cyano-3-phenoxybenzyl (1R,3S)-2,2-dimethyl-3-(2, 2-dichlorovinyl)-cyclopropane-carboxylate (5c) was prepared from (1R,3S)-2, 2-dimethyl-3-(2, 2-dichlorovinyl)-cyclopropane-carboxylic acid chloride (2c) and (−)-3-phenoxy-mandelic acid (1) as shown in Fig. 1. And the diastereoisomer (5c) was identical in the all respects with *d-trans* Cypermethrin *β*. Therefore the most active diastereoisomer (*d-trans* Cypermethrin α) must have a S configuration at the α-cyanobenzyl carbon atom.

*1 Optical purity of the resolved acid ((−)-3-phenoxy-mandelic acid) was determined by GLC analysis of the corresponding (+)-MTPA ester which was prepared from the acid with (+)-MTPC ((R)-(+)-α-methoxy-α-trifluoromethyl phenylacetic acid chloride) in usual manners and succeeding CH_2N_2 methylation of the carboxylic group.

*2 It was obtained following Elliott's method[4] from NRDC-156 or (R S)-α-cyano-3-phenoxybenzyl (IR, 3R)-2,2-dimethyl-3-(2,2-dibromovinyl)-cyclopropane-carboxylate which was synthesized from (R S)-α-cyano-3-phenoxybenzyl alcohol and (1R,3R)-2,2-dimethyl-3-(2,2-dibromovinyl)-cyclopropane-carboxylic acid chloride.

*3 Enantiomer excess ratios at the benzylic asymmetric carbon atoms were kept virtually unchanged for the acid (3a), the amide (4a) and the cyanobenzyl ester (5a) as monitored by NMR analysis.

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