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Studies on Pyrethroidal Compounds* Part V. Synthesis and Toxicity of Thermal Decomposition Products of Furamethrin. Yasuo Abe, Nobushige Itaya, Haruka Oouchi and Yoshio Fujita (Research Department, Pesticides Division, Sumitomo Chemical Co., Ltd., 4-2-1 Takatsukasa, Takarazuka City, Hyogo, Japan) Received March 5, 1975. *Botyu-Kagaku*, 40, 67, 1975.

12. ピレスロイド系化合物の研究（第5報）フラメスリン熱分解生成物の合成と毒性 安部八洲男，板谷信重，大内 晴，藤田義雄（住友化学工業株式会社生物科学研究所農薬事業部研究部）
50. 3. 5 受理

次の5種類のフラメスリン熱分解生成物を調製した：(±)-*trans*-chrysanthemic acid (I), (±)-pyrocin (II), (±)-dihydrochrysanthemolactone (III), 5-formyl-2-furylmethyl (±)-*cis, trans*-chrysanthemate (V) および 5-(2′-formylethenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VIII). VIII の合成には V をグリニアル反応によって 5-(1′-Hydroxy-2′-propenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VI) に導き，次いでハロゲンによって転位反応を併って 5-(3′-Halogeno-1′-propenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VII a, b) に導き，これを二酸化マンガンで酸化する方法がうまくいった．

調製した分解生成物および2種類の条件で加熱したフラメスリンの殺虫効力を，イエバエ，アカイエカについて油剤及び微量滴下法で評価した．分解生成物5種についてはいずれも，ノックダウン効力，致死効力ともに何ら示さず，加熱フラメスリンの殺虫力はその中に含まれるフラメスリン含量に比例していた．従って，加熱フラメスリンの殺虫力は，その中に含まれるフラメスリンによるものであると推定した．

In a previous paper[1] the authors identified five thermal decomposition products from (±)-*cis, trans*-furamethrin, which is a synthetic pyrethroid and also known as prothrin, and proposed the pathways of the pyrolysis. The decomposition products are: (±)-*trans*-chrysanthemic acid (I), (±)-pyrocin (II), (±)-dihydrochrysanthemolactone (III), 5-formyl-2-furylmethyl (±)-*cis, trans*-chrysanthemate (V) and 5-(2′-formylethenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VIII). This paper deals with syntheses of the thermal decomposition products. And also their toxicities to houseflies (*Musca domestica*) and mosquitoes (*Culex pipiens*) are examined in order to clarify the influence of heat on effectiveness of furamethrin.

Furamethrin purified by distillation was heated under two different conditions, either at 130°C for 10 hr or at 200°C for 7 hr. The temperature of the former condition is near to that of domestic electric vaporizer for anti-mosquito mat, and gave a brown viscous liquid, containing 21.5% of furamethrin. The latter condition gave a solid (*ca.* 30%) insoluble in organic solvent ($CHCl_3$, AcOEt, MeOH, DMSO and acetone) and a soluble

* Part IV; see reference (1).

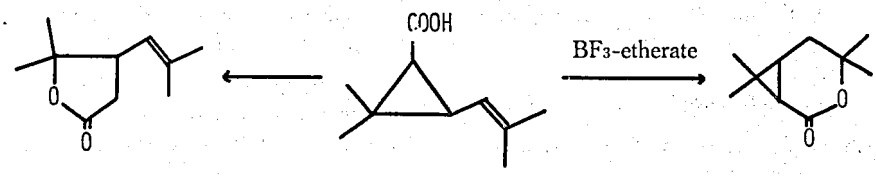


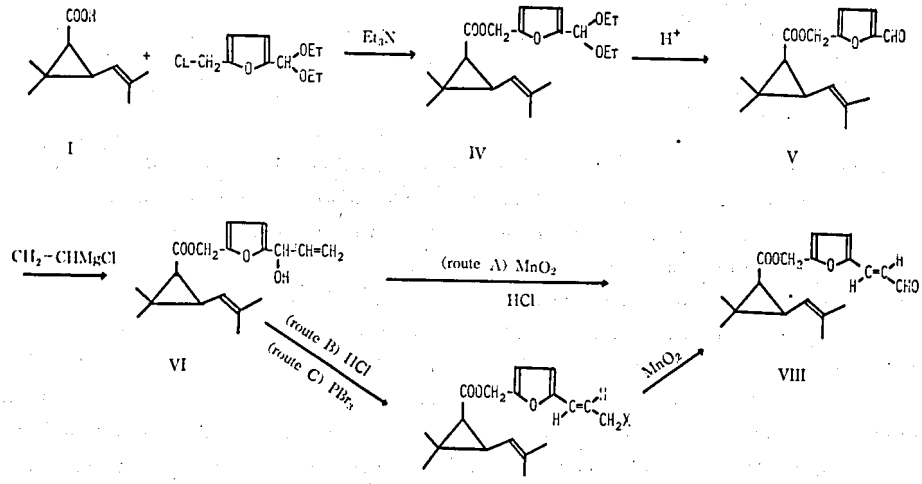
Fig. 1.

liquid (*ca.* 70%) having chrysanthemic acid-like and irritative smell. The soluble lipuid contained 37.2% of furamethrin, thus 26.1% of furamethrin was obtained without decomposition from the whole sample. Decrease of purity of furamethrin was affected more largely by heating time than by heating temperature. The ratio of *cis/trans* isomers of furamethrin was not altered by heating at different temperatures from original furamethrin.

(±)-Pyrocin (II) was obtained by heating (±)-*trans*-chrysanthemic acid in an open vessel under a nitrogen atmosphere[2]. Treatment of (±)-*cis*, *trans*-chrysanthemic acid in dichloroethane with boron trifluoride etherate gave III and (±)-*trans*-chrysanthemic acid. The latter was removed by washing with 5% sodium hydroxide solution[3].

The compound V was obtained by the reaction of 5-chloromethylfurfural diethylacetal with (±)-*cis*, *trans*-chrysanthemic acid in dimethylformamide, followed by a treatment with 6% hydrochloric acid.

5-Hydroxymethylfurylacrolein could be obtained by aldol condensation of 5-acetoxymethylfurfural with acetaldehyde[4]. It was however impossible to synthesize the ester (VIII) from 5-hydroxymethylfurylacrolein by esterifying chrysanthemic acid or its acid chloride, because of the lability of 5-hydroxymethylfurylacrolein under reaction conditions. Therefore, we tried to synthesize VIII using V as a starting material. An attempt of aldol condensation of V with acetaldehyde resulted in cleavage of the ester linkage. Preparation of VIII from diethylacetal of V (*i.e.* IV) by addition of zinc chloride in ethylacetate and ethylvinylether was unsuccessful[5]. An alternative route to synthesize VIII from V with diethyl formylmethylphosphonate diethylacetal and sodium amide in



VII a : X=Cl
b : X=Br

Fig. 2.

dry tetrahydrofuran was also unsuccessful, owing to hydrolysis of the ester linkage[6].

5-(1′-Hydroxy-2′-propenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VI) was prepared by addition of vinyl magnesium chloride to V in tetrahydrofuran in a high yield. No reaction proceeded when 4% hydrochloric acid (10m*l*) was added to an ether solution (20m*l*) of VI (1g) and the mixture was kept with stirring at room temperature during 7 hr. After reflux of chloroform solution of VI with 20% aqueous hydrochloric acid solution, the product was oxidized with activated manganese dioxide to give VIII in a satisfactory yield (route B in Fig. 2). In the product obtained after reflux of VI with 20% hydrochloric acid, absorption of hydroxyl (3395 cm^{-1}) and terminal vinyl (988, 927 cm^{-1}) group in IR spectrum disappeared and *trans*-disubstituted double bond (965 cm^{-1}) appeared. This result suggests that the product is 5-(3′-chloro-1′-propenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VIIa).

The bromination product (VIIb) of VI with phosphorus tribromide gave VIII in a high yield by oxidation with activated manganese dioxide in chloroform (route C). The bromination product was supporsed to be 5-(3′-bromo-1′-propenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VII b) by IR spectrometry (1725, 1649, 1152, 955, 854, 790 cm^{-1}), which indicated the existence of a *trans*-disubstituted double bond (955 cm^{-1}). A chloroform solution of VI was heated under reflux with 20% aqueous hydrochloric acid solution and excess activated manganese dioxide at 75°C for 3 hr, affording VIII in a low yield (route A). The lower yield of this route may be due to the possible occurence of the ester hydrolysis and the elimination of vinyl group. Formation of V as a by-product in route A was confirmed by IR and TLC. Only V and VIII were detected from the reaction mixture in route A on TLC (developing solvent; ether: *n*-hexane, 1 : 1, v/v) as brown color spots by spraying 2, 4-dinitrophenylhydrazine solution. The formation of 5-(1′-oxo-2′-propenyl)-2-furylmethyl chrysanthemate was not observed. Therefore under these reaction conditions allyl rearrangement of VI and subsequent chlorination or bromination occoured during reflux with hydrochloric acid (routes A and B) or stirring with phosphorus tribromide (route C).

It is reasonable to assume that 5-(3′-hydroxy-1′-propenyl)-2-furylmethyl chrysanthemate formed as an intermediate by hydrolysis of VIIa or VIIb would be oxidized with activated manganese dioxide. This reaction however appear to proceed successfully only with furylpropenyl halides. An oxidation of phenylpropenyl bromide with activated manganese dioxide under a similar condition was

Table 1. Effectiveness of thermal decomposition products of furamethrin and heated furamethrins by oil spray test in glass chamber.

Insect : housefly (*Musca domestica domestica*, Lab-em-7-em strain)

Material in deobase (0.2% a. i.)	Percent knockdown in minutes									KT_{50} (sec)	Mortality after 24hr (%)
	38″	53″	1′15″	1′45″	2′30″	3′30″	5′00″	7′00″	10′00″		
(±)-*trans*-Chrysanthemic acid (I)	0	0	0	0	0	0	0	0	0	*	0
(±)-Pyrocin (II)	0	0	0	0	0	0	0	0	0	*	0
(±)-Dihydrochrysanthemolactone (III)	0	0	0	0	0	0	0	0	0	*	0
5-Formyl-2-furylmethyl (±)-*cis, trans*-chrysanthemate (V)	0	0	0	0	0	0	0	0	0	*	0
5-(2′-Formylethenyl)-2-furylmethyl (±)-*cis, trans*-chrysanthemate (VIII)	0	0	0	0	0	0	0	0	0	*	0
Heated (±)-*cis, trans*-furamethrin (130°C, 10hr)	0	0	0	0	0	0	1.7	18.3	25.0	747	1.7
〃 (200°C, 7hr)	0	0	0	0	0	5.0	15.0	28.3	38.3	615	20.0
(±)-*cis, trans*-Furamethrin	0	0	0	1.7	1.7	10.0	38.3	56.7	65.0	367	43.3

* Non calculable.

unsuccessful. IR of VIIa and VIIb showed *trans*-disubstituted double bond as to configurations, and a large coupling constant (J=15.5−15.6 cps) for vicinal protons of the double bond in VIII was assigned to a formyl group *trans* to the furan ring. This suggests that *trans*-formyl group of the vinyl side chain of the furan ring is less sterically hindered than *cis*-formyl.

Toxicities of two heated samples of furamethrin described previously, except insoluble solid, and five thermal decomposition products obtained by synthesis were tested against houseflies and mosquitoes by oil spray and topical application methods.

As shown in Tables 1 and 2, neighther knockdown housefly nor mosquito was observed until after 10 min in oil spray test with five thermal decomposition products. Knockdown effect and mortal effect of a heated sample of furamethrin (130°C, 10 hr) against both insects were inferior to those of another heated sample of furamethrin (200°C, 7 hr). In topical application test (Table 3), five thermal decomposition products showed no or only low toxicity against houseflies even by the doses of 100 times as large as that of furamethrin. A lower toxicity was found with a heated sample of furamethrin (130°C, 10 hr) than with another one (200°C, 7 hr), which was consistent

Table 2. Effectiveness of thermal decomposition products of furamethrin and heated furamethrins by oil spray test in glass chamber.
Insect : mosquito (*Culex pipiens pallens*)

Material in deobase (0.2% a.i.)	Percent knockdown in minutes									KT_{50} (sec)	Mortality after 24hr (%)
	38″	53″	1′15″	1′45″	2′30″	3′30″	5′00″	7′00″	10′00″		
(±)-*trans*-Chrysanthemic acid (I)	0	0	0	0	0	0	0	0	0	*	0
(±)-Pyrocin (II)	0	0	0	0	0	0	0	0	0	*	0
(±)-Dihydrochrysanthemolactone (III)	0	0	0	0	0	0	0	0	0	*	0
5-Formyl-2-furylmethyl (±)-*cis,trans*-chrysanthemate (V)	0	0	0	0	0	0	0	0	0	*	0
5-(2′-Formylethenyl)-2-furylmethyl (±)-*cis,trans*-chrysanthemate (VIII)	0	0	0	0	0	0	0	0	0	*	0
Heated (±)-*cis,trans*-furamethrin (130°C, 10hr)	0	0	0	0	0	6.9	17.2	31.0	72.4	492	82.8
〃 (200°C, 7hr)	0	0	0	0	3.3	3.3	23.3	53.3	90.0	360	86.7
(±)-*cis,trans*-Furamethrin	0	0	0	1.0	6.7	26.7	66.7	93.3	96.7	253	96.7

* Non calculable.

Table 3. Toxicities of thermal decomposition products of furamethrin and heated furamethrins to houseflies (*Musca domestica domestica*, Lab-em-7-em strain) by topical application method.

Material	Percent kill after 24 hr	Dosage (μg/fly)
(±)-*trans*-Chrysanthemic acid (I)	0.0	30
(±)-Pyrocin (II)	3.3	30
(±)-Dihydrochrysanthemolactone (III)	2.2	30
5-Formyl-2-furylmethyl (±)-*cis,trans*-chrysanthemate (V)	0.0	30
5-(2′-Formylethenyl)-2-furylmethyl (±)-*cis,trans*-chrysanthemate (VIII)	1.1	30
Heated (±)-*cis,trans*-furamethrin (130°C, 10hr)	10.0	0.3
〃 (200°C, 7hr)	16.7	0.3
(±)-*cis,trans*-Furamethrin	56.7	0.3

with the results in oil spray. In these biological tests, EtOAc-insoluble solid produced by heating at 200°C for 7 hr was removed. Taking into account *ca.* 30% of the solid in the heated furamethrin (200°C, 7 hr) and the absence in another one (130°C, 10 hr), both treatments of heating appear to cause almost the same decrease in toxicity of furamethrin.

These biological results indicate that no thermal decomposition product contributes to knockdown effect or mortal effect, and that the toxicity of heated samples of furamethrin is parallel to the furamethrin contents in the samples. It is therefore considered that insecticidal toxicity of heated furamethrin depends only on furamethrin contained in the sample. When an anti-mosquito mat of domestic electric vaporizer is heated, vaporization of the insecticide proceeds continuously from the begining of heating and the insecticide is not heated under reflux. And practical anti-mosquito mat contain a useful stabilizer. It should be therefore said that the condition of practical use is not so severe as these experimental conditions. The authors have already confirmed that recovery of furamethrin is 75-80 % under practical condition. Thus, the decrease of toxicity by heating on the electric vaporizer under practical use will be very slight.

Experimantal

(±)-*cis, trans-Furamethrin and heated* (±)-*cis, trans-furamethrin*: Technical grade furamethrin (purity 84.9%) was purified by distillation under reduced pressure, bp. 148°C/0.4 mmHg. Purity 94.1%, ratio of *cis/trans* isomers = 20.9/79.1. The furamethrin (5g) was placed in a 100 m*l* round-bottomed flask equipped with a reflux condenser. The flask was covered with aluminum foil to shield frow light. Heating of the flask in a silicone oil bath (130°C) for 10 hr gave a brown viscous liquid, containing 21.5% of furamethrin, *cis/trans* isomers of furamethrin = 21.3/78.7. Heating of furamethrin in the flask at 200°C for 7 hr gave a EtOAc-insoluble solid (*ca.* 30%) and a EtOAc-soluble liquid (*ca.* 70%). The latter contained 37.2% of furamethrin, *cis/trans* isomers of furamethrin=22.8/77.2.

(±)-*trans-Chrysanthemic acid* (*I*): Recrystallization from petroleum ether afforded long prisms, mp 53-54°C.

(±)-*Pyrocin* (*II*): (±)-*trans*-Chrysanthemic acid was refluxed for 5 hr under nitrogen current. Recrystallization from petroleum ether afforded pale yellow crystal, mp 58-59°C. $IR\nu_{max}^{film}$ cm^{-1}: 1765, 1672, 1375, 1268, 1100, 975, 958, 935, 919.[2]

(±)-*Dihydrochrysanthemolactone* (*III*): A mixture of (±)-*cis, trans*-chrysanthemic acid (15g ; *cis/trans*=35/65) in dichloroethane (15m*l*) and boron trifluoride etherate (0.4m*l*) was kept with stirring at 60-70°C for 2 hr. After cooling, the mixture was dissolved in benzene (50m*l*) and washed with 5% aqueous sodium hydroxide solution. After drying over anhydrous magnesium sulfate, the solvent was distilled away. The residue was recrystallized from *n*-hexane, mp 52-53°C. Yield: 4.7g (90%). $IR\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1350, 1270, 1215, 1095, 1045, 955.[3]

5-Formyl-2-furylmethyl (±)-*cis, trans-chrysanthemate* (*V*): (±)-*cis, trans*-Chrysanthemic acid (34.5g) and triethyl amine (29g) in dimethylformamide and 5-chloromethylfurfural dietylacetal (44g) were mixed at 50°C. The product was treated with 6% aqueous hydrochloric acid solution to give a pale yellow solid. Yield 27.6g (50%). The solid was recrystallized from *n*-hexane to afford colorless powder, mp 54.0-55.0°C, *cis/trans* isomers=15/85. Further details of these reactions and properties (Elementary analysis, MS, IR, NMR) of the product (V) were reported in the previous paper.[1]

5-(1'-Hydroxy-2'-propenyl)-2-furylmethyl (±)-*cis, trans-chrysanthemate* (*VI*): Addition of vinyl magnesium chloride (3.3g) to V (8.5g) in tetrahydrofuran gave VI. Yield; 8.4g (90%). Further details of this reaction were reported in the previous paper.[1] $IR\nu_{max}^{liquid\ film}$ cm^{-1}: 3395, 1731, 1155, 1019, 988, 927.

5-(2'-Formylethenyl)-2-furylmethyl (±)-*cis, trans-chrysanthemate* (*VIII*):

(A) One gram of VI was dissolved in chloroform (30m*l*), and 20% aqueous hydrochloric acid solution (1m*l*) and activated manganese dioxide (3g) were added with stirring to the solution. The mixture was heated under reflux at 75°C for 3 hr. The product was purified by preparative TLC of silica gel. Developing solvent;*n*-hexane:

ether (1 : 1, v/v), R_f 0.45. Yield; 250mg (25%). $IR\nu_{max}^{liquid\ film}$ cm^{-1}: 1728, 1681, 1630, 1520, 1381, 1194, 1159, 1117, 1024, 965, 860, 810.

(B) Five hundred miligrams of VI was dissolved in chloroform (30 m*l*) and 20% aqueous hydrochloric acid solution (0.5m*l*) was added to the solution. The mixture was heated under reflux at 65°C for 6 hr. After an addition of activated manganese dioxide (1.5g), the mixture was heated under reflux at 75°C for 3 hr. The product was purified by preparative TLC of silica gel developed with *n*-hexane : ether (1 : 1, v/v) to give colorless liquid. R_f of VIII=0.45. Yield; 400 mg (80%). $IR\nu_{max}^{liquid\ film}$ cm^{-1} : 1730, 1685, 1630, 1380, 1190, 1150, 1110, 965, 855, 798. NMR $\delta_{TMS}^{CCl_4}$: 9.54 (1H, doublet, J = 7.2 cps, -CHO), 7.10 (1H, doublet, J = 15.5 cps, -CH=), 6.64 (1H, doublet, J=3.5 cps, H-C=), 6.52 (1H, double doublet, J = 7.2, 15.5 cps, =CH-), 6.39 (1H, doublet, J = 3.5 cps, H-C=), 5.00 (2H, singlet, -O-CH_2-), 4.85 (1H, double multiplet, J = 7.5 cps, -CH=), 2.03 (1H, double multiplet, J = 7.5 cps, H-C-), 1.70 (6H, singlet, CH_3-×2), 1.33 (1H, doublet, J = 4.2 cps, H-C-CO), 1.24 (3H, singlet, CH_3-), 1.14 (3H, singlet, CH_3-).

(C) After bromination of VI (11.3g) with phosphorus tribromide (6g) in absolute ether, an oxidation of the product with activated manganese dioxide (30g) in chloroform afforded a pale yellow liquid (VIII). Yield; 10.3g (92%). Further details of this reaction and some properties (Elementary analysis, MS, IR, NMR) of the product (VIII) were reported in the previous paper.[1]

Assay methods for toxicity

a) Oil spray test in glass chamber

Twenty susceptible houseflies (10 each of males and females) and 20 mosquitoes (females) were released into a glass chamber (70 cm cube). Deobase (deodorized kerosene) solution (0.7 m*l*) containing 0.2% of a test material was sprayed into glass chamber with an atomizer at the pressure of 20 psi. The knockdown insects were counted at indicated intervals up to 10 min. The mortality was observed after 24 hr.

b) Topical application test

Adult houseflies, 3 or 4 days old after emergence, were anesthetized by solid carbon dioxide, and treated with 0.5 μl of acetone solution containing test materials on the thoracic tergum using a microsyringe. The mortality was observed 24 hr later.

Summary

Five thermal decomposition products of furamethrin ; (±)-*trans*-chrysanthemic acid (I), (±)-pyrocin (II), (±)-dihydrochrysanthemolactone (III), 5-formyl-2-furylmethyl (±)-*cis*, *trans*-chrysanthemate (V) and 5-(2'-formylethenyl)-2-furylmethyl (±)-*cis*, *trans*-chrysanthemate (VIII) were prepared. The toxicities of these five compounds and two heated samples of furamethrin were examined against houseflies and mosquitoes by oil spray and topical application methods. No thermal decomposition product contributed to knockdown effect or mortality. It was found that insecticidal toxicity of heated furamethrin was based only on furamethrin contained in the sample.

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