

## Synthesis of 3,4-Methylenedioxyphenyl Ethers and their Synergistic Activities

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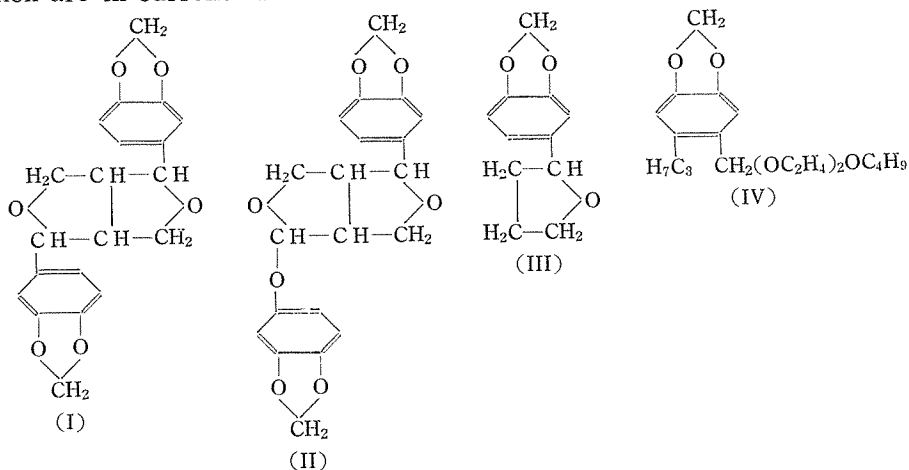
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2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuryl ether and the related compounds in which tetrahydrofuran ring is attached to the methylenedioxyphenyl group through an oxygen atom and methylene group at the 2 position of tetrahydrofuran ring have been synthesized for testing as potential synergists for pyrethrins and allethrin against common housefly, *Musca domestica vicina* Macq.

The synergistic activities were evaluated by topical application method using the micrometer syringe. Among these compounds 2-(3', 4'-methylenedioxyphenyl)-tetrahydrofuryl ether (V) was about 1.4 times as effective as piperonyl butoxide in synergistic action on pyrethrins.

In a recent study on pyrethrum synergists in sesame oil, sesamol (II)<sup>2)</sup> which had not been known previously to be synergistic was found to be about five times as active as sesamin (I) and an equiproportional mixture of sesamol and pyrethrins increasing the insecticidal value of the latter 31 times. The chemical structure of this potent synergist was determined by Beroza<sup>2)</sup>. Moreover, the synthesis of sesamin was accomplished by Beroza<sup>3)</sup> and Freudenberg<sup>4)</sup> and stereochemistry of sesamin and its stereoisomers were also studied. 2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuran (III), which has half structure of sesamin was synthesized by Kuraoka<sup>5)</sup> and the synergistic activity of this compound on allethrin was of about the same order as that of piperonyl butoxide, 3, 4-methylenedioxy-6-propylbenzyl butyl diethylene glycol ether (IV), which are in current use.

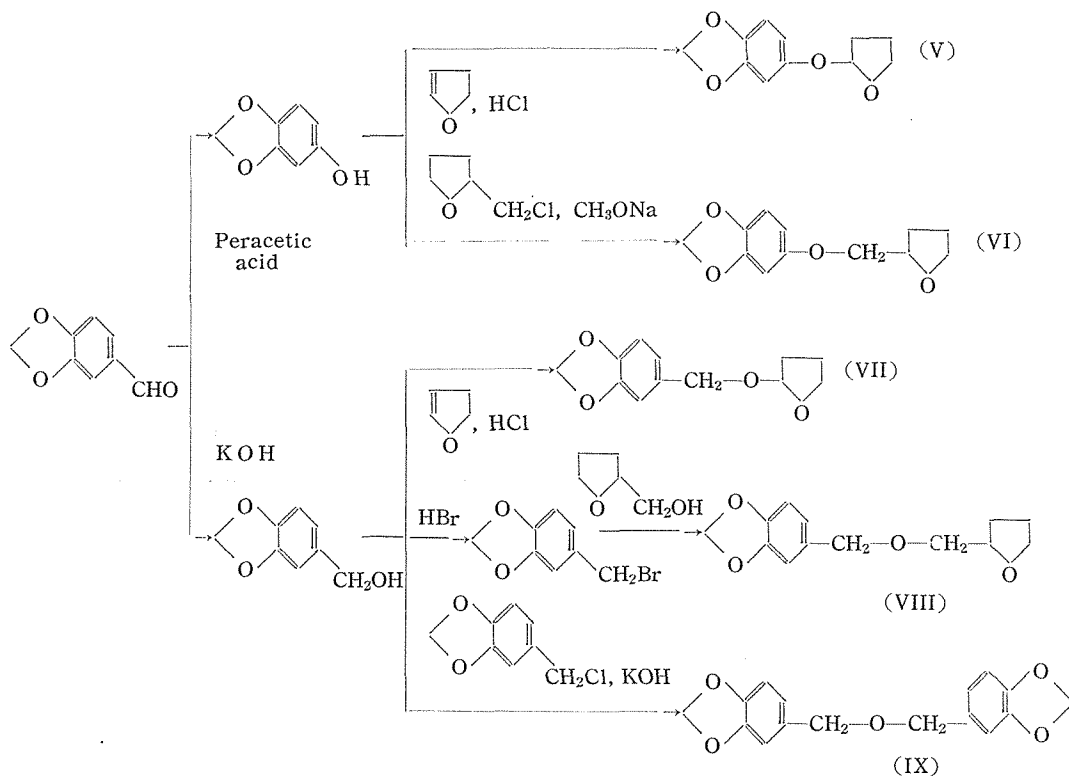


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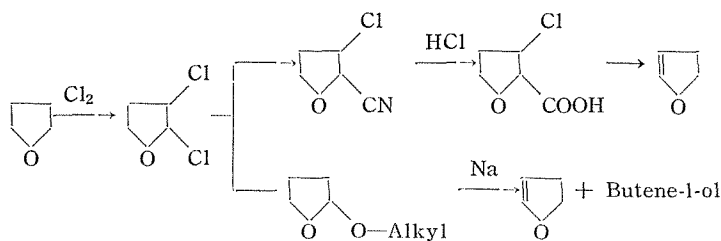
### Synthesis of 3,4-Methylenedioxyphenyl Ethers

Therefore it is of interest to study the synergistic action of 2-(3', 4'-methylenedioxyphenyl)-tetrahydrofuryl ether and the other ethers containing methylenedioxyphenyl-radical and tetrahydrofuryl- or tetrahydrofurfuryl-radical on pyrethroids.

In this paper are described, the synthesis and synergistic activity of the following several ethers (V~IX) in which the tetrahydrofuran ring is attached to the methylenedioxyphenyl group through an oxygen atom and methylene group at the 2 position of the tetrahydrofuran ring.



2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuryl ether (V) was prepared from 3,4-methylenedioxyphenol (sesamol)<sup>6)</sup> and 2,3-dihydrofuran in the presence of trace concentrated hydrochloric acid. Sesamol used was synthesized in 65% yield by the reaction of piperonal with 20% peracetic acid which was prepared from 88% hydrogen peroxide and acetic acid. In this reaction, when



13.5% peracetic acid obtained from 30% hydrogen peroxide was used, the yield of sesamol was very low. 2, 3-Dihydrofuran was previously prepared through 2-alkoxy-3-chloro-tetrahydrofuran by Normant's<sup>7,8)</sup> method. But in this process butene-1-ol was much obtained. So it was found the following process was more suitable than the above process to prepare 2, 3-dihydrofuran.<sup>9)</sup>

2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofurfuryl ether (VI) was prepared by the condensation of tetrahydrofurfuryl chloride with sesamol in a sealed tube. 2-Piperonyl-tetrahydrofuryl ether (VII) which is isomeric with (VI) was prepared from piperonyl alcohol and 2,3-dihydrofuran. 2-Piperonyl-tetrahydrofurfuryl ether (VIII) was obtained by heating piperonyl bromide and tetrahydrofurfuryl alcohol with metallic sodium. Di-piperonyl ether (IX) was also prepared by heating piperonyl chloride and piperonyl alcohol with potassium hydroxide.

2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuran (III) was prepared according to Kuraoka's method<sup>5)</sup>.

The synergistic activities of these compounds with pyrethrins or allethrin against the common housefly, *Musca domestica vicina* Macq., were evaluated by topical application method using the micrometer syringe. The relative effec-

Table 1. Relative synergistic effectiveness of synthetic ethers on pyrethrins as compared with piperonyl butoxide.

Entry	Material	Relative knockdown effectiveness after 30 min. (Calcd. from $KD_{50}$ ).	Relative lethal effectiveness after 24 hrs. (Calcd. from $LD_{50}$ ).
IV	Piperonyl butoxide	1.00	1.00
III	2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuran	1.25	1.26
V	2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuryl ether	1.39	1.48
VI	2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofurfuryl ether	0.22	0.24
VII	2-Piperonyl-tetrahydrofuryl ether	0.22	0.35
VIII	2-Piperonyl-tetrahydrofurfuryl ether	0.30	0.45
IX	Di-piperonyl ether	0.13	0.27

Table 2. Relative synergistic effectiveness of synthetic ethers on allethrin as compared with piperonyl butoxide.

Entry	Material	Relative knockdown effectiveness after 30 min. (Calcd. from $KD_{50}$ ).	Relative lethal effectiveness after 24 hrs. (Calcd. from $LD_{50}$ ).
IV	Piperonyl butoxide	1.00	1.00
V	2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuryl ether	1.09	1.02
III	2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuran	1.10	1.07

## Synthesis of 3, 4-Methylenedioxyphenyl Ethers

tiveness of these compounds as compared with piperonyl butoxide are shown in Tables 1 and 2.

Among these seven compounds, 2-(3', 4'-methylenedioxyphenyl)-tetrahydrofuryl ether was the most effective. This is a more active synergist than the synergists in current use.

### EXPERIMENTAL

**3, 4-Methylenedioxyphenol (sesamol).** To a stirred solution of 90 g. of 34% peracetic acid (prepared from 50 g. of glacial acetic acid, 45 g. of 88% hydrogen peroxide and 0.55 ml. of concentrated sulfuric acid), maintained at 35-40°, a mixture of 135 g. of acetic anhydride and 108 g. of acetic acid was added during 6 hrs. The slow addition is necessary to avoid the formation of acetyl peroxide. After standing for 16 hrs. at 25°, 2.8 g. of sodium acetate and 1.6 g. of p-toluenesulfonic acid were added. To a stirred solution of 125 g. of piperonal in 650 g. of acetic acid, maintained at 30-40° was added the above resultant solution during 7 hrs. After additional 12 hrs., peroxide in the product was absolutely negative. After removal of the solvent under reduced pressure, distillation gave a yellow oil, bp. 135°/5mm. Yield 115 g. The distillate was added to 76 g. of potassium hydroxide dissolved in 684 g. of methanol and maintained at 25° for 3 hrs. Then, 66 g. of acetic acid was added to neutralize the alkali and the solvents were distilled off. The residual oil was taken up in 400 g. of ethylenedichloride, washed with water containing 0.5% of sodium sulfite and dried over anhydrous sodium sulfate. Distillation gave colorless oil, bp. 113-6°/2mm. Crystallization of the crude sesamol from toluene and then from a mixture of toluene and chloroform gave colorless plates, mp. 62°. Yield 87 g. (65%).

**2-Cyano-3-chloro-tetrahydrofuran.** A mixture of 125 g. of 2, 3-dichlorotetrahydrofuran, 83 g. of dried cuprous cyanide and 130 ml. of xylene was heated at 140° for 3 hrs. After cooling, the cuprous chloride was filtered off and the solvent was removed. Distillation gave a colorless liquid, bp. 79-93°/14mm. Yield 79 g. (63%).

**3-Chlorotetrahydrofuroic acid.** Under vigorous stirring, 30 ml. of concentrated hydrochloric acid was added through the dropping funnel to 30 g. of 3-cyano-2-chloro-tetrahydrofuran. After cooling, the mixture was extracted with ether, washed with water and dried over sodium sulfate. After removal of the solvent, the reaction product solidified. Recrystallisation from benzene gave colorless plates, mp. 92°. Yield 25 g. (76%).

**2. 3-Dihydrofuran.** A mixture of 150 ml. of 2N-potassium hydroxide and 20 g. of 3-chlorotetrahydrofuroic acid was heated in the modified Claisen flask. The 2. 3-dihydrofuran formed gradually distilled over. Distillation of crude 2. 3-dihydrofuran gave a colorless liquid, bp. 54-5°. Yield 8.3 g. (84%).

**2-(3', 4'-Methylenedioxyphenyl)-tetrahydrofuryl ether (V).** To a mixture of 1.4 g. of 2,3-dihydrofuran and a few drops of concentrated hydrochloric acid were gradually added 2.7 g. of sesamol. When the addition of sesamol was

over, a pellet of potassium hydroxide was added to the reaction product to neutralize the hydrochloric acid. Distillation gave a colorless oil, bp. 126-128°/1.5mm. Yield 2.8 g. (70%).

For further purification, the above ether was dissolved in ether, washed with aqueous potassium hydroxide and water, dried over anhydrous sodium sulfate and distilled under reduced pressure, bp. 127°/1.5mm.  $n_D^{25}$  1.5395. *Anal.* Calcd. for  $C_{11}H_{12}O_4$  : C, 63.45 : H, 5.81. Found : C, 63.36 : H, 5.88.

**2-(3',4'-Methylenedioxyphenyl)-tetrahydrofurfuryl ether (VI).** 1.38 g. of sesamol was dissolved in a 5 ml. of 10% methanolic solution of sodium methoxide. To this solution was added 1.3 g. of tetrahydrofurfuryl chloride and heated in a sealed tube at 160° for 3 hrs. The reaction product was taken up in ether, washed with water and dried over anhydrous sodium sulfate. Distillation gave a colorless oil, bp. 143-4°/1.5mm. Yield 0.6 g. (27%).  $n_D^{25}$  1.5379. *Anal.* Calcd. for  $C_{12}H_{14}O_4$  : C, 64.85 : H, 6.35. Found : C, 65.44 : H, 6.04.

**2-Piperonyl-tetrahydrofurfuryl ether (VII).** To a mixture of 1.4g. of 2, 3-dihydrofuran and 3.0 g. of piperonyl alcohol was added a few drops of concentrated hydrochloric acid. After standing for 3 hrs. at room temperature, a pellet of potassium hydroxide was added to the reaction product to neutralize the hydrochloric acid. Distillation gave a colorless oil, bp. 133-5°/1.5mm. Yield 3.8 g. (86%).  $n_D^{25}$  1.5286. *Anal.* Calcd. for  $C_{12}H_{14}O_4$  : C, 64.85 : H, 6.35. Found : C, 64.62 : H, 6.47.

**2-Piperonyl-tetrahydrofurfuryl ether (VIII).** A 1.2 g. quantity of sodium metal was dissolved in 10 g. of tetrahydrofurfuryl alcohol. To this solution was added 15 g. of piperonyl bromide and the mixture was refluxed for 2 hrs. until the sodium bromide ceased to form. The reaction product poured into water and extracted with ether, washed with water and dried over anhydrous sodium sulfate. Distillation gave a colorless oil, bp. 142-3°/1mm. Yield 11 g. (68%).  $n_D^{25}$  1.5275. *Anal.* Calcd. for  $C_{13}H_{16}O_4$  : C, 66.08 : H, 6.83 Found : C, 66.04 : H, 6.87.

**Di-piperonyl-ether (IX).** A mixture of 2.6 g. of piperonyl alcohol, 2 g. of piperonyl chloride and 1.8 g. of potassium hydroxide pellets was heated at 200° for 3 hrs. The reaction product was dissolved in ether, washed with water and dried over anhydrous sodium sulfate. After removal of ether, distillation gave a colorless oil, bp. 189-92°/0.5mm. Yield 3.1 g. (78%). Recrystallisation from chloroform and n-hexane gave colorless needles, mp. 41°. *Anal.* Calcd. for  $C_{16}H_{14}O_5$  : C, 67.12 : H, 4.93 : Found : C, 66.89 : H : 4.66.

**3-Piperonylideneopropanol.** A mixture of 120 g. of safrole and 50 g. of paraformaldehyde was heated in an autoclave at 200-230° (10 atoms) for 4 hrs. The reaction product was then heated at 110° to remove the unreacted paraformaldehyde and then fractionated under reduced pressure, bp. 150-170°/5mm. Pale yellow distillate gradually solidified. Recrystallization from carbon tetrachloride gave colorless plates, mp. 59°. Yield 30 g. (23%).

**2-(3',4'-Methylenedioxyphenyl)-tetrahydrofuran (III).** Hydrogen chloride gas, dried passing through concentrated sulfuric acid, was introduced into a ether solution of 7 g. of 3-piperonylideneopropanol for 3 hrs. After removal of

### Synthesis of 3,4-Methylenedioxyphenyl Ethers

the unreacted hydrogen chloride gas, the reaction product was added gradually to 80 ml. of 13% ethanolic potassium hydroxide solution. Potassium chloride formed was filtered and the solvent was removed. Residual oil was dissolved in ether, washed with water and dried over anhydrous sodium sulfate. Distillation gave a colorless oil, bp. 115-7°/1.5mm. Yield 4.3 g. (61%).  $n_D^{25}$  1.5470. *Anal.* Calcd. for  $C_{11}H_{12}O_3$ : C, 68.73; H, 6.29; Found: C, 68.69; H, 6.31.

**Bio-assay.** Acetone solutions of several concentration were prepared as containing pyrethrins plus ten times of amounts of the above mentioned newly synthesized synergists (V-IX) and (III-IV). As for allethrin were examined only (III-V) which showed relatively high synergistic effect on pyrethrins. In every case, pip. butoxide plus active ingredient solution was used as the standard.

The adults of common housefly, *Musca domestica vicina* Macq., 4-5 days after emergence were used. The synergistic activities of these mixtures were evaluated by topical application method using the micrometer syringe. To each insect adopted 0.0005 ml. of the above acetone solution. Percentage of knock-down after 30 min. and percentage of mortality after 24 hrs. were recorded and the relative synergistic effectiveness of the above compounds were calculated from their median knockdown dose and median lethal dose. They are summarized in Tables 1 and 2.

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