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The Synthesis of 3-Piperonyltetrahydrofuran

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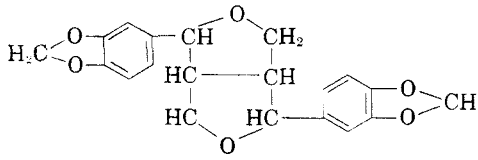
3-Piperonyltetrahydrofuran and 10 related compounds have been synthesized for testing as potential synergists for pyrethrins against house flies.

Sesamin (I) increases the effectiveness of pyrethrins as a fly spray[1] without itself showing any toxic action. In seeking other synergistic materials of this type, which are more soluble in the hydrocarbon solvents in common use, LaForge and coworkers[2] attempted the synthesis of the half-sesamin molecule (II). They prepared *alpha*-(3-chloropropyl)piperonyl alcohol (III), but all attempts to cyclize III and related compounds resulted in the formation of *alpha*-allylpiperonyl alcohol (IV) instead of the corresponding furan (II). It seems that the difficulty in the synthesis of II may be due to molecular strain, since the corresponding pyran (V), which is an effective synergist for pyrethrins, was synthesized[3] in three steps from piperonal, ethyl acetate, and trimethylene bromide.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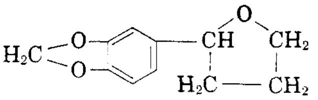
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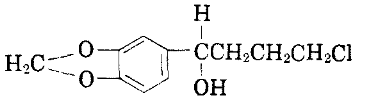
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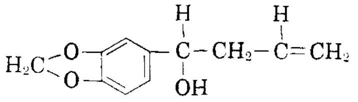
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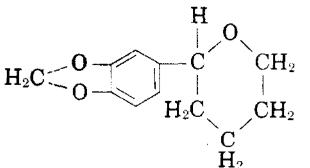
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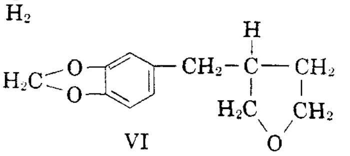
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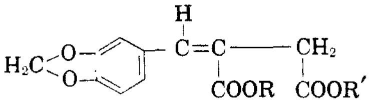
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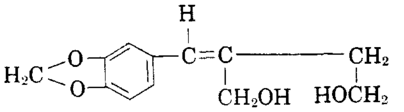
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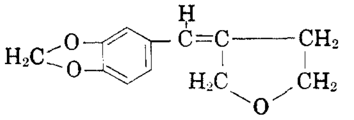
IX

This paper outlines the synthesis of the substituted compound VI, in which the furan ring is attached to the methylenedioxyphenyl group through a methylene group at the 3 position of the furan ring. It also describes the synthesis of several related diesters of piperonylidene and piperonylsuccinic acid which were of interest since these compounds had not been previously reported and their insecticidal activity was unknown.

The monoethyl ester of piperonylidenesuccinic acid (VII, $R = H, R' = C_2H_5$) was prepared as described by Cornforth, Hughes, and Lions.[4] The monomethyl, monopropyl, diethyl, and dipropyl esters of piperonylidenesuccinic acid (VII, R = H, alkyl; R′ = alkyl) were synthesized also, as well as similar esters of piperonylsuccinic acid by hydrogenation of VII. Lithium aluminum hydride reduction of the monoesters or diesters of VII gave the unsaturated 2-piperonylidene-1,4-butanediol (VIII) in 85% yield. This was surprising, since Nystrom and Brown[5] reported that cinnamic acid on treatment with lithium aluminum hydride undergoes concurrent reduction at the double bond producing hydrocinnamyl alcohol. When the 2-piperonylidene-1,4-butanediol (VIII) was dissolved in ether and treated with dry hydrogen chloride at 0° or refluxed with 6% methanolic hydrogen chloride, 3-

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(1) Haller, LaForge, and Sullivan, *J. Org. Chem.*, **7**, 185 (1942); Beroza and Schechter, *J. Am. Chem. Soc.*, *in press.*

(2) LaForge, Barthel, and Bendigo, *unpublished work.*

(3) LaForge, U. S. Patent 2,421,570 (1947).

(4) Cornforth, Hughes, and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 228 (1938).

(5) Nystrom and Brown, *J. Am. Chem. Soc.*, **69**, 2548, 1197 (1947).

piperonylidenetetrahydrofuran (IX) was produced. Hydrogenation of IX at 1 atmosphere with a platinum oxide catalyst yielded 3-piperonyltetrahydrofuran (VI).

An attempt was made to synthesize VI by the following series of reactions: Diethyl piperonylidenesuccinate (VII) was hydrogenated under pressure with a nickel-kieselguhr catalyst,[6] and the resulting diester was reduced with lithium aluminum hydride to piperonylbutanediol (VIII saturated at double bond). When 2-piperonyl-1,4-butanediol was dissolved in ether and treated with hydrogen chloride or refluxed with methanolic hydrogen chloride, a mixture of compounds isomeric with VI resulted.

EXPERIMENTAL

The monomethyl ester of piperonylidenesuccinic acid (VII, R = H, R′ = CH_3) was prepared by the method of Cornforth, Hughes, and Lions;[4] m.p. 136–138° recrystallized from benzene; yield 56%.

Anal. Calc'd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.17; H, 4.59.

The dimethyl ester of piperonylidenesuccinic acid (VII, R and R′ = CH_3) was prepared from the monomethyl ester by refluxing with methanol containing 6% sulfuric acid; m.p. 83–84° recrystallized from methanol; yield 59%.

Anal. Calc'd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.39; H, 5.01.

The diethyl ester of piperonylidenesuccinic acid (VII, R and R′ = C_2H_5) was prepared as described for the dimethyl ester above or *via* the acid chloride; b.p. 184–191°/0.3 mm.; n_D^{25} 1.5512; yield 29% *via* the acid chloride or 59% by the former procedure.

Anal. Calc'd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 63.49; H, 6.20.

The monopropyl ester of piperonylidenesuccinic acid (VII, R = H, R′ = C_3H_7) was prepared by the method of Cornforth, *et al.*;[4] m.p. 120–121° recrystallized from benzene; yield 51%.

Anal. Calc'd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.85; H, 5.24.

The dimethyl ester of piperonylsuccinic acid was prepared by hydrogenating the unsaturated ester (VII) in alcohol, with a nickel-kieselguhr catalyst,[6] under pressure; b.p. 160–163°/0.3 mm.; n_D^{25} 1.5133; yield 91%.

Anal. Calc'd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.76. Found: C, 60.04; H, 5.55.

The diethyl ester of piperonylsuccinic acid was prepared as described for the dimethyl ester above; b.p. 159–164°/0.3 mm.; n_D^{25} 1.5032; yield 89%.

Anal. Calc'd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.27; H, 6.39.

The dipropyl ester of piperonylsuccinic acid was prepared as above; b.p. 180–186°/0.04 mm.; n_D^{25} 1.4947; yield 90%.

Anal. Calc'd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.32.

2-Piperonylidene-1,4-butanediol (VIII). Diethyl piperonylidenesuccinate was reduced with lithium aluminum hydride;[5] m.p. 85–86° recrystallized from benzene; yield 85%. The compound reduced a 1% potassium permanganate solution.

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.10; H, 6.44.

2-Piperonyl-1,4-butanediol. 2-Piperonylidene-1,4-butanediol (VIII) was dissolved in alcohol and hydrogenated with a nickel-kieselguhr catalyst, under pressure; b.p. 190°/0.6 mm.; n_D^{25} 1.5493; yield 92%.

Anal. Calc'd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.29; H, 7.40.

3-Piperonylidenetetrahydrofuran (IX). 2-Piperonylidene-1,4-butanediol (VIII), 6 g., was refluxed in 200 ml. of 6% methanolic hydrogen chloride for 6 hours. After standing at 5° overnight, the solution was neutralized with 5% sodium carbonate and concentrated *in vacuo* to one-third the original volume, which then was extracted with ether and the ether layer washed with cold water. After removal of the ether, the residue was distilled; b.p. 135–137°/1.3 mm.; n_D^{25} 1.5603; yield 65%. This compound gave no test for active hydrogen with Grignard reagent (Zerewitinoff method), but it reduced a 1% potassium permanganate solution.

Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 69.86; H, 5.77.

3-Piperonyltetrahydrofuran (VI). Piperonylidenetetrahydrofuran (IX), 2 g., was dissolved in alcohol. A platinum oxide catalyst, 0.1 g., was added and the mixture was hydrogenated at one atmosphere. After removal of solvent the residue was distilled; b.p. 108°/1 mm.; n_D^{25} 1.5380; yield 70%. This compound gave no test for active hydrogen nor did it reduce potassium permanganate solution.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.93; H, 7.01.

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[6] Covert, Connor, and Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932).