

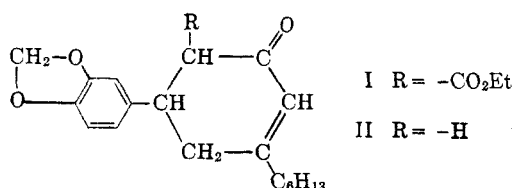
## Analogs of "Piperonyl Cyclonene"

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Some substituted 5-aryl-3-methyl-2-cyclohexene-1-ones have been prepared because of their relationship to the insecticide and synergist "piperonyl cyclonene." The method of synthesis involves the conversion of substituted ethyl benzal-bis-acetoacetates to 5-aryl-4-carbethoxy-3-methyl-2-cyclohexene-1-ones, followed by saponification and decarboxylation to give 5-aryl-3-methyl-2-cyclohexene-1-ones.

The successful non-toxic insecticide and synergist for pyrethrins called "piperonyl cyclonene" is a mixture of 6-carbethoxy-5-piperonyl-3-*n*-hexyl-2-cyclohexene-1-one (I) and 5-piperonyl-3-*n*-hexyl-2-cyclohexene-1-one (II).<sup>1,2</sup>

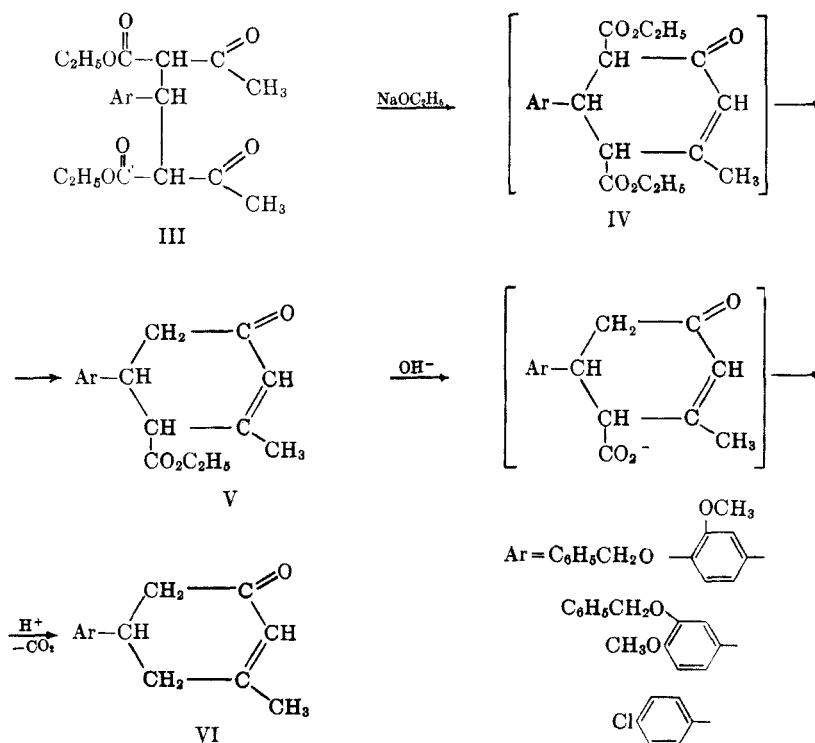


This paper reports the preparation of certain analogs of "piperonyl cyclonene" in which the hexyl group is replaced by methyl and in which the methylenedioxy substituent in the aromatic ring is replaced by other ether groups or by chlorine.

These analogs still contain the conjugated system  $\text{—C=CHC=O}$  which, according to some reports,<sup>2</sup> is essential for insecticidal activity in this series of compounds.

The desired compounds were prepared by the following sequence of reactions.

The bis-acetoacetates (III) were prepared by the piperidine catalyzed condensation of ethyl acetoacetate with the appropriate aromatic aldehydes according to previously described procedures.<sup>3</sup> The inclusion of the 4,6-dicarbethoxy derivative (IV) as an intermediate in the sequence of reactions seems justified, since a small amount of 5-benzylvanillyl-4,6-dicarbethoxy-3-methyl-2-cyclohexene-1-one was isolated from the mother liquor from the recrystallization of 5-benzylvanillyl-4-carbethoxy-3-methyl-2-cyclohexene-1-one.



(1) Wachs, Jones, and Bass, *New Safe Insecticides, Advances in Chem. Ser.*, No. 1, p. 43.

(2) Hedenberg and Wachs, *J. Am. Chem. Soc.*, **70**, 2216 (1948).

(3) Smith and Kort, *J. Am. Chem. Soc.*, **72**, 1877 (1950).

The yield in the cyclization step (III  $\rightarrow$  V) was about 35% in each case studied. The yields in the decarboxylation of V varied from 58% to 77%.

The yield of crude product from the cyclization step is good, but large losses in recrystallization result in the low yield of V. The over-all yield of VI from III can be improved (at least where Ar = benzylvanillyl) by only partly purifying the 5-benzylvanillyl-4-carbomethoxy-3-methyl-2-cyclohexene-1-one before submitting it to the next step. In this way 5-benzylvanillyl-3-methyl-2-cyclohexene-1-one was obtained in 47% yield from ethyl benzylvanillal-*bis*-acetoacetate. This compares very favorably with the 26.5% yield obtained when the intermediate (V) is purified completely before going to the next step. It is likely that these increases in yield could be obtained in the other cases when the intermediate 4-carbomethoxy derivative is not also wanted. It is necessary to partly purify V by one or two recrystallizations before proceeding to the next step. If this partial purification is not first carried out, the next step (V  $\rightarrow$  VI) is entirely unsuccessful.

Substitution of 95% ethanol for absolute ethanol in the cyclization reaction does not affect the yield. Also, the amount of sodium used in this reaction can be varied without appreciably altering either the course of the reaction or the yield. In the majority of the experiments, the molar ratio of *bis*-ester to sodium was 1:1; ratios of *bis*-ester to sodium of 1:0.1 and 1:2 gave reaction mixtures which were generally oily and more difficult to crystallize.

The ultraviolet absorption spectra of 5-benzylvanillyl-4-carbomethoxy-3-methyl-2-cyclohexene-1-one, 5-benzylvanillyl-3-methyl-2-cyclohexene-1-one and 5-benzylisovanillyl-3-methyl-2-cyclohexene-1-one show strong absorption at 2275–2300 Angstroms and a slightly weaker absorption at 2800–2815 Angstroms. These results are consistent with the  $\alpha,\beta$ -unsaturated ketone structure of the compounds.

The substituted cyclohexenones reported here show little or no insecticidal activity when tested against the house fly, army worm, bean beetle larva, mealy worm bug, and aphid. The piperonyl derivatives exhibit a mild fungicidal activity and the *p*-chlorophenyl derivatives a weak fungicidal activity when tested by the slide germination technique against *Alternaria oleracea*, *Glomerella cingulata*, and *Monolinia fructicola*.

#### EXPERIMENTAL

*5-Benzylvanillyl-4-carbomethoxy-3-methyl-2-cyclohexene-1-one*  
To a solution of 2.5 g. (0.11 mole) of sodium in 330 ml. of absolute ethanol was added 53 g. (0.11 mole) of ethyl benzylvanillal-*bis*-acetoacetate, and the mixture was refluxed for five hours. The orange solution was poured into 500 ml. of water containing 20 ml. of concentrated hydrochloric acid to give 42 g. of yellow oil which solidified on standing overnight. Recrystallizations from 95% ethanol yielded 15 g. (34.5%) of white product melting at 122–123°.

*Anal.* Calc'd for  $C_{21}H_{26}O_6$ : C, 73.09; H, 6.64. Found: C, 72.83; H, 6.59.

The yellow *p*-nitrophenylhydrazone<sup>4</sup> melted at 178.5–180° after recrystallization from 95% ethanol.

*Anal.* Calc'd for  $C_{30}H_{31}N_3O_6$ : C, 68.03; H, 5.90; N, 7.93. Found: C, 67.98; H, 5.89; N, 8.06.

*5-Benzylvanillyl-3-methyl-2-cyclohexene-1-one. Method A.*  
A solution of 6.5 g. (0.016 mole) of 5-benzylvanillyl-4-carbomethoxy-3-methyl-2-cyclohexene-1-one in 50 ml. of 95% ethanol was added to 30 ml. of water containing 4 g. of sodium hydroxide; the mixture was refluxed for 30 minutes, cooled to room temperature, acidified with about 20 ml. of 1:1 hydrochloric acid and refluxed for an additional 15 minutes. At the end of the reflux period the tan mixture was poured into 300 ml. of cold water to precipitate 6 g. of tan solid, m.p. 98–102°. Repeated recrystallizations from 95% ethanol, and treatment with Norit, yielded 4.2 g. (77%) of very light tan crystals, m.p. 106.5–108°.

*Anal.* Calc'd for  $C_{21}H_{22}O_3$ : C, 78.24; H, 6.88. Found: C, 78.15; H, 6.87.

The red *2,4-dinitrophenylhydrazone*<sup>4</sup> was purified by recrystallization from mixtures of 95% ethanol, chloroform, and ethyl acetate and melted at 166–168°.

*Anal.* Calc'd for  $C_{27}H_{26}N_4O_6$ : C, 64.53; H, 5.21; N, 11.15. Found: C, 64.39; H, 5.36; N, 11.01.

*5-Benzylvanillyl-3-methyl-2-cyclohexene-1-one. Method B.*  
A solution of 24 g. (0.05 mole) of ethyl benzylvanillal-*bis*-acetoacetate in 300 ml. of absolute ethanol containing 0.23 g. (0.01 mole) of sodium was refluxed for five hours. At the end of the reflux period the pale yellow mixture was poured into 500 ml. of ice-water. The yellow oil solidified on standing. The solid was recrystallized twice from 95% ethanol (once using Norit) to give 13 g. of a pale yellow solid, m.p. 98–110°. This material then was added to a solution of 8 g. of sodium hydroxide in 60 ml. of water and 100 ml. of 95% ethanol and was refluxed for one-half hour. The orange solution was cooled to room temperature, acidified with 1:1 hydrochloric acid and refluxed an additional 15 minutes. Upon pouring the solution into cold water, 12.5 g. (78%) of a tan solid precipitated, m.p. 100–105°. Recrystallizations from 95% ethanol gave 7.5 g. (47%) of light tan crystals, m.p. 106.5–108°.

*5-Benzylvanillyl-4,6-dicarbomethoxy-3-methyl-2-cyclohexene-1-one.* The mother liquors from the recrystallizations of 5-benzylvanillyl-4-carbomethoxy-3-methyl-2-cyclohexene-1-one were combined and concentrated in an effort to obtain additional product. Upon concentration, a white crystalline solid, m.p. 150–156° separated. The purified material melted at 159–161°. A mixture melting point with ethyl benzylvanillal-*bis*-acetoacetate (which also melts at 159–161°) was 154–155°.

*Anal.* Calc'd for  $C_{27}H_{30}O_7$ : C, 69.50; H, 6.48. Found: C, 69.58; H, 6.57.

The yellow *2,4-dinitrophenylhydrazone*,<sup>4</sup> m.p. 209–211°, was recrystallized from a mixture of chloroform, 95% ethanol, and ethyl acetate.

*Anal.* Calc'd for  $C_{33}H_{34}N_4O_{10}$ : C, 61.30; H, 5.30; N, 8.66. Found: C, 61.48; H, 5.33; N, 8.70.

*5-Benzylisovanillyl-4-carbomethoxy-3-methyl-2-cyclohexene-1-one.* A solution of 34 g. (0.07 mole) of ethyl benzylisovanillal-*bis*-acetoacetate in 210 ml. of absolute ethanol containing 1.6 g. (0.07 mole) of sodium was refluxed for five hours. The orange solution was poured into 250 ml. of ice-water containing 10 ml. of concentrated hydrochloric acid. The yellow oil which separated did not solidify on standing. It was dissolved in a mixture of 50 ml. of ethyl acetate and 75 ml. of petroleum ether (b.p. 60–70°) and cooled to give 12 g. of slightly yellow solid, melting at about 75–76°. Subsequent recrystallizations gave 9 g. (34.5%) of white product melting at 85–87°.

(4) Shriner and Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, New York, 1948, p. 171.

*Anal.* Calc'd for  $C_{24}H_{26}O_5$ : C, 73.09; H, 6.64. Found: C, 72.97; H, 6.61.

The yellow *p*-nitrophenylhydrazone<sup>4</sup> melted at 139–139.5° after recrystallization from 95% ethanol.

*Anal.* Calc'd for  $C_{30}H_{31}N_3O_6$ : C, 68.03; H, 5.90; N, 7.93. Found: C, 68.05; H, 5.93; N, 7.85.

*5-Benzylisovanillyl-3-methyl-2-cyclohexene-1-one.* A solution of 7 g. (0.018 mole) of 5-benzylisovanillyl-4-carbethoxy-3-methyl-2-cyclohexene-1-one in 35 ml. of 95% ethanol was added to 40 ml. of water containing 4 g. of sodium hydroxide and was refluxed for 40 minutes. The reaction mixture was cooled to room temperature, acidified with 20 ml. of 1:1 hydrochloric acid, and refluxed 15 minutes. On pouring the mixture into 350 ml. of ice-water, 5.5 g. of dark tan solid separated, m.p. 72–75°. The solid was recrystallized four times (once with the addition of Norit) from small amounts of absolute ethanol to give 3.8 g. (66%) of salmon-pink crystals, m.p. 73.5–75°.

*Anal.* Calc'd for  $C_{21}H_{22}O_3$ : C, 78.24; H, 6.88. Found: C, 78.02; H, 6.75.

The yellow-orange 2,4-dinitrophenylhydrazone<sup>4</sup> melted at 175–176° after recrystallization from a mixture of 95% ethanol and ethyl acetate.

*Anal.* Calc'd for  $C_{27}H_{26}N_4O_6$ : C, 64.53; H, 5.21; N, 11.15. Found: C, 64.68; H, 4.97; N, 11.27.

*5-p-Chlorophenyl-4-carbethoxy-3-methyl-2-cyclohexene-1-*

*one.* To a solution of 0.8 g. (0.035 mole) of sodium in 100 ml. of absolute ethanol was added 16.5 g. (0.043 mole) of ethyl *p*-chlorobenzal-bis-acetoacetate. The mixture was refluxed for five hours and then poured into 80 ml. of ice-water containing 5 ml. of concentrated hydrochloric acid. The oil which separated partly solidified on cooling. The supernatant liquid was decanted and the residue was recrystallized from isopropyl alcohol to give 4.5 g. (35%) of white product melting at 81.5–82.5°.

*Anal.* Calc'd for  $C_{19}H_{17}ClO_3$ : C, 65.60; H, 5.86. Found: C, 66.04; H, 5.81.

*5-p-Chlorophenyl-3-methyl-2-cyclohexene-1-one.* A solution of 7.4 g. (0.025 mole) of 5-*p*-chlorophenyl-4-carbethoxy-3-methyl-2-cyclohexene-1-one in 58 ml. of 95% ethanol was added to a solution of 4.7 g. of sodium hydroxide in 35 ml. of water. The mixture was refluxed for one-half hour, cooled to room temperature, and acidified with 1:1 hydrochloric acid. The mixture then was refluxed for 15 minutes and poured into 300 ml. of water. The solid which separated weighed 5.5 g. After two recrystallizations from 95% ethanol there was obtained 3.2 g. (58%) melting at 54–55°.

*Anal.* Calc'd for  $C_{13}H_{13}ClO$ : C, 70.70; H, 5.92. Found: C, 70.76; H, 5.95.

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