Synthesis of Compounds with Juvenile Hormone Activity

Part IV.* Methyl ($\pm$)-14-Homojuvenate** and its *4*²-*cis* Isomer, Analogues of *Cecropia* Juvenile Hormone

By Kenji MORI, Masahiko OHKI, B. STALLA-BOURDILLON,
Masanao MATSUI and William S. BOWERS***

Department of Agricultural Chemistry, Faculty of Agriculture,
University of Tokyo, Bunkyo-ku, Tokyo

Received June 4, 1969

Recent elucidation of the chemical structure of C_{18} -*cecropia* juvenile hormone (I) by Röllner *et al.*¹⁾ was a remarkable achievement in the chemical studies on insect metamorphosis.

Since then three non-stereoselective^{2~4)} and three stereoselective^{5~7)} syntheses of the hormone have been reported as well as an extensive survey on the structure-activity relationship with synthetic analogues.⁸⁾ On the other hand Meyer, Schneidermann *et al.*^{9,10)}

isolated a new juvenile hormone from the silk moth, *Hyalophora cecropia*, and assigned the structure II to it (C_{17} -*cecropia* juvenile hormone,

* Part III, K. Mori, T. Miyake, I. Yoshimura and M. Matsui, *Agr. Biol. Chem.*, **33**, 1745 (1969).

** For this nomenclature see ref. 10.

*** Entomology Research Division, USDA Agricultural Research Service, Beltsville, Maryland, U.S.A.

1) H. Röllner, K. H. Dahm, C. C. Sweeley and B. M. Trost, *Angew. Chem. Intern. Ed.*, **6**, 179 (1967).

2) K. H. Dahm, B. M. Trost and H. Röllner, *J. Am. Chem. Soc.*, **89**, 5292 (1967).

3) B. H. Braun, M. Jacobson, M. Schwarz, P. E. Sonnet, N. Wakabayashi and R. M. Waters, *J. Econ. Entomol.*, **61**, 866 (1968).

4) K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui and W. S. Bowers, *Tetrahedron*, **25**, 1667 (1969).

5) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968).

6) R. Zurflüh, E. N. Wall, J. B. Siddall and J. A. Edwards, *ibid.*, **90**, 6224 (1968).

7) W. S. Johnson, Tsung-tee Li, D. J. Faulkner and S. F. Campbell, *ibid.*, **90**, 6225 (1968).

8) V. B. Wigglesworth, *J. Insect Physiol.*, **15**, 73 (1969).

9) A. S. Meyer, H. A. Schneidermann and E. Hanzmann, *Fed. Proc.*, **27**, 393 (1968).

10) A. S. Meyer, H. A. Schneidermann, E. Hanzmann and J. H. Ko, *Proc. Nat. Acad. Sci. U.S.A.*, **60**, 853 (1968).

methyl 12-homojuvenate).

Inspection of the structures I and II made us to assume that methyl ($\pm$)-14-homojuvenate (VI) might possess the same degree of juvenile hormone activity as II. Here we describe its synthesis together with that of its Δ^2 -*cis* isomer (V). This is the extension of our previous work on the synthesis of a mixture of V and VI.⁴¹

The mixture of methyl *cis*, *trans*- and *trans*, *trans*-7-ethyl-3,11-dimethyl-2,6,10-dodecatrienates (III and IV in 1:4 ratio)⁴¹ was separated by preparative gas-liquid chromatography to give pure esters III and IV. The infrared and nuclear magnetic resonance spectra of the two esters were similar to but not identical with each other. The C-3 methyl protons of the *cis*-isomer (III) absorbed at $\delta=1.85$ ppm while those of the *trans*-isomer (IV) at $\delta=2.12$ ppm. These values are in good accord with those reported for the analogous intermediates.²¹ Epoxidation of the ester IV with *m*-chloroperbenzoic acid in methylene chloride followed by thin layer chromatographic purification afforded the desired epoxy ester (VI) with reasonable spectral data. Similar treatment of the *cis*-isomer (III) gave the isomeric epoxy ester (V).

The juvenile hormone activity of the two esters (V and VI) was tested on freshly molted pupae of the yellow mealworm, *Tenebrio molitor* L. Complete juvenilization, that is, molting to second pupae, signaled extremely high activity, while pupal-adult intermediates were observed with less active samples. Low activi-

ty was indicated by the retention of nearly pupal genitalia in an otherwise normal beetle. The results are shown in the Table. Although the both isomers are biologically active, the *trans*, *trans*-epoxy ester (VI, methyl ($\pm$)-14-homojuvenate) is considerably more active than the corresponding *cis*, *trans*-isomer (V). This emphasizes the importance of the *trans* double bond at C-2 for biological activity.^{cf. 8)}

EXPERIMENTAL

Separation of methyl trans, trans-7-ethyl-3,11-dimethyl-2,6,10-dodecatrienate (IV) from the Δ^2 -cis isomer (III). Gas chromatographic analysis of the mixture of III and IV revealed that it could be separated by preparative gas chromatography. Retention time: 7.3 min for III (20%) 8.4 min for IV (80%); Column, SE 30, 2 m $\times$ 3 mm *i.d.*; Column temp. 190°C; Carrier gas, He 20 ml/min. The conditions employed for the separation were: Column, Silicon oil DC 200 (20%) on Celite 545 (60–80 mesh), 10 ft $\times$ 3/8 inch; Column temp., 230°C; carrier gas, He, 35 kg/cm². From 1.7 g of the mixture; 130 mg of III and 300 mg of IV were obtained. The *trans*, *trans*-ester (IV) was distilled *in vacuo* to give a pure product, n_D^{18} 1.4818. Anal. Found: C, 77.57; H, 11.01. Calcd. for C₁₇H₁₈O₂: C, 77.22; H, 10.67%. $\nu_{\max}$ (film) 1720, 1645, 1430, 1370, 1350, 1220, 1180 cm⁻¹; δ (ppm from TMS at 100 MHz, in CCl₄) 0.96 (3H, t, *J*=6Hz), 1.57 (3H, s), 1.65 (3H, s), 2.12 (3H, s), 3.56 (3H, s), 4.95 (2H, broad), 5.52 (1H, s). Gas chromatographic analysis of IV by capillary columns (45 m $\times$ 0.5 mm *i.d.*): (i) Castor wax, 190°C, N₂ (0.5 kg/cm²), retention time 26.2 min. (ii) FS-1265, 190°C, N₂ (0.5 kg/cm²), retention time 41.6 min. (iii) SE-30, 190°C, N₂ (0.5 kg/cm²), retention time 9.4 min. The *cis*-isomer (III) exhibited the following spectral properties: $\nu_{\max}$ (film) 1725, 1650, 1430, 1370, 1230, 1185, 1150 cm⁻¹; δ (ppm from TMS at 100 MHz, in CCl₄) 0.96 (3H, t, *J*=6Hz), 1.56 (3H, s), 1.63 (3H, s), 1.85 (3H, s), 3.54 (3H, s), 5.00 (2H, broad), 5.49 (1H, s).

Methyl ($\pm$)-14-homojuvenate (VI) and its Δ^2 -cis isomer (V). A solution of the pure Δ^2 -*trans* ester (IV, 172 mg, 0.65×10^{-3} mole) in methylene chloride (5 ml) was mixed with a solution of *m*-chloroperbenzoic acid (112 mg, 0.65×10^{-3} mole) in methylene chloride (10 ml). The mixture was left to stand at 0–5°C for 18 hr

TABLE. JUVENILE HORMONE ACTIVITY OF THE SYNTHETIC PRODUCTS

	The <i>cis</i> , <i>trans</i> - epoxy ester (V)	Methyl ($\pm$)-14- homojuvenate (VI)
0.01 μ g	inactive	inactive
0.1	inactive	partially pupal genitalia
1.0	inactive	pupal-adult intermediates
10.0	complete second pupae	complete second pupae

and then poured into saturated sodium bicarbonate solution. The organic layer was separated, washed with sodium bicarbonate solution and water, and dried over magnesium sulfate. Removal of the solvent gave crude oily epoxy ester (VI, 175 mg). This was purified by preparative thin layer chromatography (Kiesel-gel G, 20 cm $\times$ 20 cm $\times$ 0.5 mm) employing ethyl acetate-benzene (1:15) as solvents to give methyl ($\pm$)-14-homojuvenate (45 mg), ν_{max} (film) 1720, 1645, 1430, 1380, 1360, 1225, 1150 cm^{-1} ; δ (ppm from TMS at 100 MHz, in CCl_4) 0.97 (3H, t, $J=6\text{Hz}$), 1.20 (3H, s), 1.23 (3H, s), 2.12 (3H, s), 2.45 (1H, t, $J=6\text{Hz}$), 3.55 (3H, s), 5.00 (1H, broad), 5.50 (1H, s); M^+ 280. This was chromatographed on a Carbowax 4000 column at 170°C as a homogeneous compound and retained at a ratio of 0.87 relative to the natural methyl 12-homojuvenate. This analysis was kindly carried out by Professor A. S. Meyer.

By the same procedure, Δ^2 -cis epoxy ester (V, 18 mg) was obtained from the Δ^2 -cis ester (III, 94 mg). The spectral properties of V are: ν_{max} (film) 1725, 1650,

1440, 1380, 1240, 1160 cm^{-1} ; δ (ppm from TMS at 100 MHz, in CCl_4) 0.99 (3H, t, $J=6\text{Hz}$), 1.20 (3H, s), 1.25 (3H, s), 1.86 (3H, s), 3.57 (3H, s), 5.08 (1H, t, $J=7\text{Hz}$), 5.52 (1H, s); M^+ 280.

Bioassay. Test compounds were applied topically to freshly molted pupae of *Tenebrio molitor* in 1 μl of acetone and they were held until the final molt toward the adult form when juvenile hormone activity is signaled by the presence of immature characters. Ten insects were used per assay. The results are summarized in the text. A preliminary bioassay by the *Galleria* wax test kindly performed by Professor A. S. Meyer confirmed the high juvenile hormone activity of methyl ($\pm$)-14-homojuvenate (VI).

Acknowledgements. We are indebted to Dr. H. Kurihara, Takasago Perfume Industry Co., Tokyo, for his help in gas chromatographic separation. Our thanks are due to Professors A. S. Meyer and H. A. Schneidermann for discussions and help.