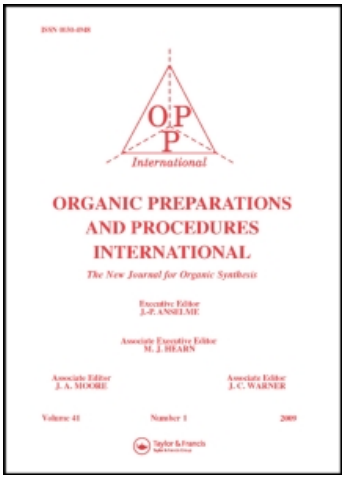


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# 7-ETHOXY-6-METHOXY-2,2-DIMETHYL-2H-1-BENZOPYRAN

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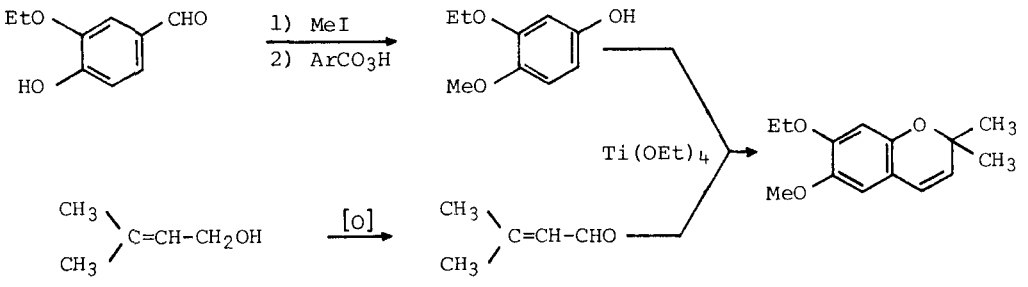
7-Methoxy- and 6,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (precocenes 1 and 2) induce precocious metamorphosis and inhibition of egg production by the milkweed bug.[1] Precocene 2 causes degeneration[2] or inhibited development[3] of the corpora allata, thereby preventing juvenile hormone (JH)secretion. The title compound (precocene 3) has over ten times higher activity than precocene 2.[4] As pheromone production by the bark beetle, Ips paraconfusus, is controlled by JH,[5] we hypothesized that precocene treatment would inhibit this process.

In order to test this hypothesis, 7-ethoxy-6-methoxy-2,2-dimethyl-2H-1-benzopyran (precocene 3) was synthesized from commercially available 3-ethoxy-4-hydroxybenzaldehyde and 3-methyl-2-buten-1-ol by the new route shown.



## EXPERIMENTAL

3-Ethoxy-4-methoxybenzaldehyde. - The procedure described for the preparation of veratraldehyde[6] was followed. 3-Ethoxy-4-hydroxybenzaldehyde (45.0 g, 0.250 mol), contained in a 200-mL three-necked flask equipped with a mechanical stirrer, a reflux condenser and two addition funnels, was melted on a steam bath; then 36.0 mL (0.375 mol) of 10.4 M KOH and 30.0 mL (0.317 mol) of dimethyl sulfate (pre-washed with 35 mL of ice-water and 12 mL of 5% aq. $NaHCO_3$) were added simultaneously to the rapidly stirred, hot liquid over a period of 20 min. After an additional ten min. of stirring at 85°, the hot reaction mixture (two clear yellow-brownish layers) was poured into a beaker and allowed to cool overnight. The hard, crystalline mass was ground in a mortar with ice-water (2 × 60 mL), washed with 25 mL of cold water, filtered with suction and dried in a vacuum desiccator ($CaCl_2$) to give 41.2 g (91.5%) of beige 3-ethoxy-4-methoxybenzaldehyde, mp. 49-51°, lit.[7] 48°, which was used without purification for the next step.
NMR($CDCl_3$): δ 9.83 (s, 1H, -CHO), 7.40 (m, 2H, 2,6-H), 6.93 (d, 1H, J 9.5 Hz, 5-H), 4.15 (q, 2H, J 7 Hz, $MeC\underline{H}_2O$-), 3.93 (s, 3H, $CH_3O$-) and 1.47 (t, 3H, J 7 Hz, $C\underline{H}_3CH_2O$-).

3-Ethoxy-4-methoxyphenol. - A solution of 9.00 g (50.0 mmol) of 3-ethoxy-4-methoxybenzaldehyde in 100 mL of $CH_2Cl_2$ (reagent-grade, pre-dried over $CaCl_2$) was added dropwise to a magnetically stirred solution of 17.50 g (approx. 86 mmol) of m-chloroperbenzoic acid (80-90%, Aldrich)[8] in 225 mL of dry $CH_2Cl_2$ and the orange-yellow mixture was refluxed for 42 hrs. The yellow solid left after removal of most of the dichloromethane in vacuo was dissolved in 200 mL of ethyl acetate,

washed with 5% aqueous $NaHCO_3$ solution (6 x 70 mL) and brine (2 x 50 mL) and dried ($Na_2SO_4$). Evaporation of the solvent in vacuo and air-drying of the solid residue gave 8.28 g (84.5%) of crude 3-ethoxy-4-methoxyphenyl formate, as white needles, mp. 66-67° (from 95% EtOH).

NMR($CDCl_3$): δ 8.22 (s, 1H, -OCHO), 6.67 (m, 3H, aromatic hydrogens), 4.03 (q, 2H, J 7 Hz, $MeCH_2O$-), 3.80 (s, 3H, $-OCH_3$) and 1.42 (t, 3H, J 7 Hz, $CH_3CH_2O$-). Mass spectrum (70 eV): m/e (relative ion intensities) 196 (30.0), 168 (19.5), 140 (24.4), 125 (100.0), 111 (11.6), 97 (18.2).

The formate ester (6.47 g, 35.0 mmol) was dissolved in 160 mL of methanol and hydrolyzed under nitrogen with 105 mL of 10% NaOH (294 mmol). After 1.5 hr. of stirring at room temperature, the black-brown solution was cooled in ice and acidified (pH 2) under nitrogen with 3N HCl leading to the formation of a beige, flocculent precipitate suspended in a yellow-orange solution. Evaporation of 180 mL of solvent in vacuo, followed by extraction with ethyl acetate (3 x 80 mL), washing of the organic layers (2 x 100 mL brine, 3 x 70 mL 5% $NaHCO_3$, 120 mL brine), drying ($MgSO_4$) and evaporation of the ethyl acetate gave 4.74 g (80.6%) of crude 3-ethoxy-4-methoxyphenol (air-dried), which was recrystallized from benzene and water/methanol (9:1 v/v) to yield 3.78 g (64%) of pure product as slightly pink needles, mp. 79-81°, lit.[7] 77-78°.

NMR($CH_3CO_2D$): δ 6.72 (d, 5-H, J 8.5 Hz), 6.43 (d, 2-H, J 2.7 Hz), 6.30 (dd, 6-H, $J_{62}$ 2.7 Hz, $J_{65}$ 8.5 Hz), 3.97 (q, 2H, J 7 Hz, $MeCH_2O$-), 3.72 (s, 3H, $CH_3O$-) and 1.35 (t, 3H, J 7 Hz, $CH_3CH_2O$-). The compound is only sparingly soluble in deuterated chloroform.

3-Methyl-2-butenal. - Chromic acid on anion exchange resin, prepared from 90 g of $CrO_3$ and 210 g of Amberlyst A-26,[9] was added to a solution of 4.75 g (55.2 mmol) of 3-methyl-2-buten-1-ol (Aldrich) in 400 mL of methylene chloride, and the mixture was refluxed for 48 hrs. Filtration, solvent evaporation and fractional distillation (under $N_2$) at atmospheric pressure gave 2.67 g of crude 3-methyl-2-butenal, bp. 125-130°, containing approximately 15% (by vpc) unreacted alcohol.

7-Ethoxy-6-methoxy-2,2-dimethyl-2H-1-benzopyran (precocene-3). - The procedure of Sartori and coworkers[10] was followed. Titanium(IV) ethoxide (1.14 g, 5.00 mmol) in 7 mL of dry toluene was added by syringe (under nitrogen) to a magnetically stirred suspension of 3.36 g (20.0 mmol) of 3-ethoxy-4-methoxyphenol in 20 mL of dry toluene. The orange-red mixture was heated at reflux (74-82°) for 30 min and the ethanol was removed slowly (50 min) by azeotropic distillation, causing a rise of the reflux temperature to 106°. A solution of 1.88 g of 3-methyl-2-butenal (approximately 85% pure, see above) in 35 mL of toluene was then added dropwise (15 min) with stirring (under nitrogen) at room temperature and, after dilution with another 40 mL of toluene, the deep red mixture was heated at reflux for 14.5 hrs. The reaction was quenched with 20% aqueous $NH_4Cl$ (100 mL) and dilute HCl (50 mL), extracted with ether (200 mL) and ethyl acetate (200 mL) and washed with 5% aqueous NaOH and brine. After drying ($MgSO_4$) and evaporation of the solvents in vacuo 3.30 g of a brown oily residue was obtained. Purification by flash distillation (bp. 109°/0.1 torr) and column chromatography on Florisil (elution with hexane/ether 9:1 v/v) yielded 1.78 g (40%) of precocene-3.

NMR($CDCl_3$): δ 6.50 and 6.38 (s, 5- and 8-H), 6.20 (d, J 9.4 Hz, 4-H), 5.43 (d, J 9.4 Hz, 3-H), 4.03 (q, 2H, J 7 Hz, $MeC\underline{H}_2O$-), and 1.38 (s, overlapping with the center peak of the EtOH triplet, 6H, $Me_2C<$); mass spectrum (70 eV) m/e (relative intensity) 234 (27.9), 220 (14.1), 219 (100.0), 191 (64.4), 176 (23.5) and 149 (10.9). The cycloaddition of 3-methyl-2-butenal could conceivably have involved the 2-position of 3-ethoxy-4-methoxyphenol leading to the formation of 5-ethoxy-6-methoxy-2,2-dimethyl-2H-1-benzopyran. However, this isomer was detected neither by nmr nor by vpc (one peak only on 1.5 m X 3 mm 5% OV-17 on Varoport at 195°, and on a 38-m OV-101 capillary column at 180°).

Bioassay: I. paraconfusus males were exposed for 24 hrs. to a surface treated with 30 $\mu g/cm^2$ of precocene 1, 2 or 3, and then fed for 24 hrs in ponderosa pine. Pentane extracts of their abdomens were analyzed on an SP-1000 glass capillary column (30 m × 0.66 mm ID). Precocene 2 almost completely inhibited production of the pheromones ipsenol and ipsdienol. Precocene 3 reduced ipsdienol content from 40 to 9 ng/beetle; precocene 1 had no effect. These results implicate the corpora allata in the control of pheromone synthesis.



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