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Synthesis of Insect Antijuvenile Hormones

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An efficient synthesis of 2,2-dimethylchromenes was developed to pursue chemical structure-biological activity studies of insect antijuvenile hormones. The combination of Michael condensation and cyclodehydration with polyphosphoric acid gave nearly quantitative yields of alkoxy 2,2-dimethylchromanones which were reduced and dehydrated in one flask, to yield the respective 2,2-dimethylchromenes. By these methods several AJH analogs were prepared which possessed greater biological activity than the natural precocenes.

Keywords—insect antijuvenile hormone; precocene; 2,2-dimethylchromene; one step synthesis of 2,2-dimethylchromanones; 6-methoxy-7-ethoxy-2,2-dimethylchromene

Two simple substituted chromenes, precocenes I and II, isolated from *Ageratum Houstonianum* (Compositae) were shown to possess insect antijuvenile hormone (AJH) activity.²⁾

Since these compounds induce precocious metamorphosis and sterilize certain insects, we have investigated the chemical structure-biological activity relationships with a view to developing more active AJH analogs. For these studies efficient synthetic methods were required. Certain 2,2-dimethylchromenes have been synthesized by several procedures³⁾ but generally in poor yield. Cyclization of aryl propargyl ethers⁴⁾ appears generally applicable to chromen synthesis, but neither Hug, *et al.*⁵⁾ nor we were able to obtain 2,2-dimethylchromenes in reported yields because of the inefficiency in preparation of tertiary carbinyl ethers.

Our synthetic approach resulted in a one step synthesis of 2,2-dimethylchromanones (3) through a combination of Michael type condensation and cyclodehydration with polyphosphoric acid. On stirring *m*-methoxyphenol and β,β -dimethylacrylic acid with polyphosphoric acid on a steam bath for 1 hr, 7-methoxy-2,2-dimethylchromanone (3: R=H, R'=OCH₃) was

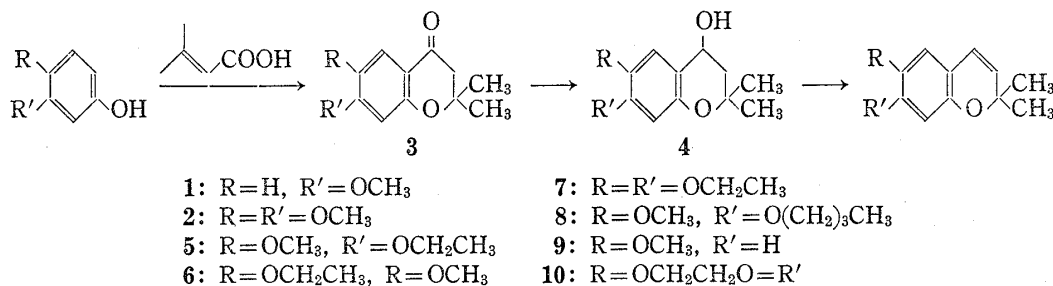


Chart 1

- 1) Location: Geneva, New York 14456, U.S.A.; a) Present address: Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, 980, Japan.
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- 4) J. Hlubucek, E. Ritchie and W.C. Taylor, *Tetrahedron Lett.* **1969**, 1369.
- 5) R. Hug, G. Frater, H.J. Hansen and H. Schmid, *Helv. Chim. Acta*, **54**, 306 (1971).

obtained in nearly quantitative yield. The chromanone (**3**: $R=H, R'=OCH_3$) was reduced with excess lithium aluminum hydride in anhydrous tetrahydrofuran and dehydration was effected without isolation of the chromanol (**4**: $R=H, R'=OCH_3$) by adding 4*N* hydrochloric acid and stirring briefly to afford 7-methoxy-2,2-dimethylchromene [precocene I (**1**)], bp 97—100°/2 mmHg, in 60% yield. Precocene II (**2**), bp 145—150°/4 mmHg, was also prepared in 81% yield from 3,4-dimethoxyphenol.

It should be noted that the yield of 6-methoxy-2,2-dimethylchromanone (**3**: $R=OCH_3, R'=H$) was only 18% when *p*-methoxyphenol and β, β -dimethylacrylic acid were treated with polyphosphoric acid at 140° for 1 hr. From these results, it is clear that the C₆ position of the phenol must be activated by a substituent at C₃ to permit a successful condensation.

Among AJH active chromenes given by the above procedure, 6-methoxy-7-ethoxy-2,2-dimethylchromene (**5**) was found to have over ten times higher activity than that of **2** in milkweed bug (*Oncopeltus fasciatus*).⁶⁾

Experimental

Alkoxyphenols—All alkoxyphenols except *m*- and *p*-methoxyphenol were prepared by oxidation of alkoxy benzaldehydes with 15.6% peracetic acid in acetic acid according to the method of Beroza.⁷⁾

Alkoxy 2,2-Dimethylchromenes—Alkoxyphenol (50 mmol) and β, β -dimethylacrylic acid (55 mmol) were stirred with 100 g of polyphosphoric acid on a steam bath for 1 hr. The reaction mixture was poured into 200 ml of ice-water and extracted with ether. The ether layer was washed with 5% sodium hydroxide solution, water, saturated brine, and dried over sodium sulfate. Evaporation of the ether gave crude chromanone (—95% pure on gas chromatography). The crude chromanone in 200 ml of anhydrous tetrahydrofuran was refluxed with 0.6 g of lithium aluminum hydride for 1 hr. Following decomposition of excess of lithium aluminum hydride with a few ml of ethyl acetate, the mixture was stirred with 100 ml of 4*N* hydrochloric acid at room temperature for 15 min and then extracted with petroleum ether (bp 30—60°). The petroleum ether layer was washed with 5% sodium hydroxide solution, water, saturated brine, and dried over sodium sulfate. Removal of the solvent *in vacuo* gave an oil which was chromatographed on 100 g of Florisil. The product was eluted stepwise with increasing concentration of ether in hexane. Overall isolated yields are given in Table I. The structures of all new substances described in Chart 1 were consistent with spectroscopic data.

TABLE I. Synthesis of 2,2-Dimethylchromenes

Phenol	Chromene No.	Yield %
3-Methoxy	1 ^{a)}	60
3,4-Dimethoxy	2 ^{b)}	81
3-Ethoxy-4-methoxy	5 ^{c)}	68
3-Methoxy-4-ethoxy	6 ^{c)}	69
3,4-Diethoxy	7 ^{c)}	60
3-Butyloxy-4-methoxy	8 ^{c)}	74
4-Methoxy	9 ^{a, d, e)}	10
3,4-Ethylenedioxy	10 ^{c)}	60

a) Recovered from the fraction eluted with 2% ether in hexane.

b) Recovered from the fraction eluted with 5% ether in hexane.

c) Recovered from the fraction eluted with 10% ether in hexane.

d) R. Livingstone and R. B. Watson, *J. Chem. Soc.*, **1957**, 1509.

e) **9** did not show an AJH activity.

6) Bioassay results will be reported elsewhere.

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