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Synthesis of Insect Antijuvenile Hormones

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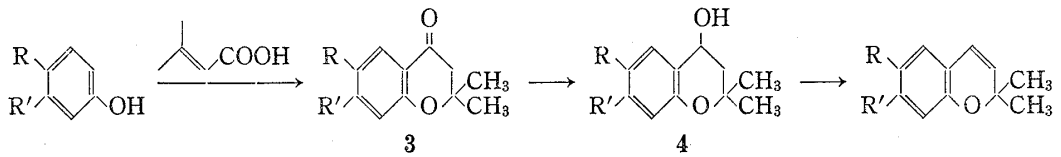
An efficient synthesis of 2,2-dimethylchromenes was developed to pursue chemical structure-biological activity studies of insect antijuvenile hormones. The combination of Michael condensation and cyclodehydration with polyphosphoric acid gave nearly quantitative yields of alkoxy 2,2-dimethylchromanones 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 procedures[3] but generally in poor yield. Cyclization of aryl propargyl ethers[4] 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′=OCH_3) was



3 4

1: R=H, R′=OCH_3
2: R=R′=OCH_3
5: R=OCH_3, R′=OCH_2CH_3
6: R=OCH_2CH_3, R=OCH_3
7: R=R′=OCH_2CH_3
8: R=OCH_3, R′=$O(CH_2)_3CH_3$
9: R=OCH_3, R′=H
10: R=OCH_2CH_2O=R′

Chart 1

1) Location: *Geneva, New York 14456, U.S.A.*; a) Present address: *Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, 980, Japan.*
2) W.S. Bowers, T. Ohta, J.S. Cleere and P.A. Marsella, *Science*, **193**, 542 (1976).
3) R.L. Shiner and A.G. Sharp, *J. Org. Chem.*, **4**, 575 (1939); L.I. Smith and P. M Ruoft, *J. Am. Chem. Soc.*, **62**, 145 (1940); R. Huls and S. Brunell, *Bull. Soc. Chim. Belg.*, **68**, 325 (1959); J. Nikcl, *Chem. Ber.*, **92**, 1989 (1959); E.E. Schweizer, E.T. Shaffer, C.T. Hughes and C.J. Berninger, *J. Org. Chem.*, **31**, 2907 (1966); G. Cardillo, R. Cricchio and L. Merlini, *Tetrahedron*, **24**, 4825 (1968); R. Mechoulam, B. Yaghitinsky and Y. Gaoni, *J. Am. Chem. Soc.*, **90**, 2418 (1968).
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 4N 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 C_6 position of the phenol must be activated by a substituent at C_3 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 4N 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.
7) M. Beroza, *J. Agr. Food Chem.*, **4**, 49 (1956).