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SYNTHESIS OF 2,2-DIMETHYL-2*H*-CHROMENES

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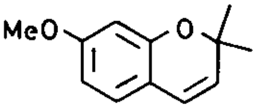
Abstract —— The antijuvenile hormones precocenes I and II (**1**,**2**), and related 2,2-dimethyl-2*H*-chromenes (**12**,**13**) were synthesized by oxidative cyclization of *o*-isoprenylphenols with *m*-chloroperbenzoic acid, followed by dehydration of the corresponding 3-chromanols with methyltriphenoxyphosphonium iodide.

Precocene I (7-methoxy-2,2-dimethyl-2*H*-chromene, **1**) and precocene II (6,7-dimethoxy-2,2-dimethyl-2*H*-chromene, **2**) isolated from the plant *Ageratum houstonianum*[1] are potentially useful insect antijuvenile hormone. Owing to this attractive biological property, several synthetic methods have been reported[2].



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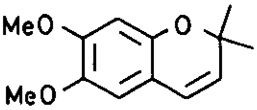

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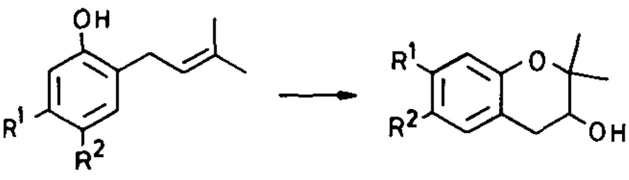
In continuation of our studies on the synthesis of biologically active natural products[3,4], we wish to report an alternative method for the synthesis of precocenes and related chromenes by oxidative cyclization[5] of *o*-isoprenylphenols and subsequent dehydration.

The *o*-isoprenylphenols **3**,**4**,**5** and **6** were prepared according to Yamada's method[6].

Compound **5** was more conveniently obtained by isoprenylation of methoxyhydroquinone with 2-methylbut-3-en-2-ol in aqueous formic acid[7].

The oxidative cyclization of substrates **3-6** were performed with *m*-chloroperbenzoic acid in methylene chloride solution at 0°C. Catalytic amounts of concentrated hydrochloric acid were added in order to avoid the formation of 2,3-dihydrobenzofurans[8] and maximize the production of 2,2-dimethyl-3-chromanols **7-10** (Scheme 1).



3−6 **7−10**

	R^1	R^2
3,7	H	OMe
4,8	OMe	H
5,9	OMe	OH
6,10	O-CH$_2$-O	

Scheme 1

Yields and spectral properties of chromanols **7-10** prepared under these conditions are described in Table 1.

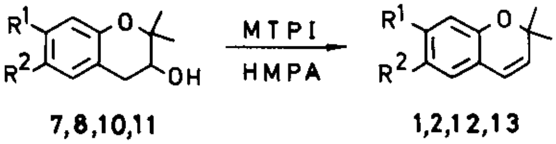
Table 1. Chromanols obtained by oxidative cyclization of *o*-prenylphenols 3 → 6.

Substance	Yield(%)	I.r.spectra(ν cm^{-1})^a	^{1}H-nmr spectra(δ ppm)^b	M.spectra;m/z(%)
7	40	3310, 1490, 1370, 1360	1.32(s,3H), 1.36(s,3H), 2.09(br s,1H), 2.72(dd, 1H,J=17;5Hz), 3.06(dd, 1H,J=17;5Hz), 3.66-3.92 (m,1H), 3.78(s,3H), 6.5-6.9(m,3H).	M$^+$208(100), 175 (49), 137(96)
8	81	3450, 1620, 1580, 1500, 1445, 1380, 1365	1.34(s,3H), 1.38(s,3H), 1.83(br s,1H), 2.69(dd, 1H,J=16;5Hz), 3.03(dd,1H, J=17;5Hz), 3.7-3.9(m,1H), 3.79(s,3H), 6.44(s,1H,J=13Hz), 6.53(dd,1H,J=8;3Hz), 6.98(d,1H,J=8Hz).	M$^+$208(29), 175 (5), 137(100)
9	32	3450, 1510, 1375br	1.32(s,3H), 1.38(s,3H), 1.74(br s,1H), 2.66(dd, 1H,J=17;5Hz), 3.01(dd,1H, J=17;5Hz), 3.6-4.0(m,1H), 3.88(s,3H), 5.26(br s,1H), 6.44(s,1H), 6.64(s,1H)	M$^+$224(34), 191 (7), 154(14), 153(100)
10	90	3515, 1630, 1480, 1390, 1380	1.31(s,3H), 1.37(s,3H), 1.82(br s,1H), 2.66(dd,1H, J=17;5Hz), 3.01(dd,1H,J=17; 5Hz), 3.76(t,1H,J=5Hz),5.91 (s,2H), 6.43(s,1H), 6.54(s, 1H)	M$^+$ 222(29), 189 (6), 152(12), 151(100)

a. Obtained in KBr (**7**,**9**,**10**) and neat (**8**); b. Performed in CDCl$_3$ solution using TMS as internal standard.

Attempted dehydration of chromanol **7** by means of a variety of reagents ($POCl_3$/Py; TsCl/Py and DMF; MsCl/Py and DMF) gave only low conversions (10-45%). Better results were obtained by reaction of **7** with methyltriphenoxyphosphonioum iodide[9] in dry HMPA solution, to afford the chromene **12** in 80% yield. In view of this, dehydration of chromanol **8**,**10** and **11** were carried out using this procedure. The results obtained are summarized in Table 2.

Table 2. 2,2-Dimethyl-2*H*-chromenes prepared by dehydration of chromanols.



Substrate	Chromene[10]	R^1	R^2	Yield (%)
7	**12**	H	OMe	80
8	**1**	OMe	H	81
10	**13**	O-CH_2O		45^b
11[a]	**2**	OMe	OMe	55^b

a. Compound **11** was obtained by methylation of **9** with Me_2SO_4-KOH;
b. No attempts were made to improve yields.

Experimental details of this chromene synthesis will be reported in a forthcoming paper.

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