NOVEL SYNTHETIC APPROACH TO ALKYLENEDIOXY- PRECOCENES

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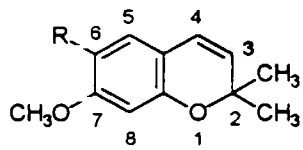
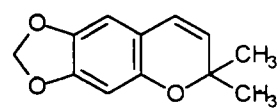
Abstract: A novel synthetic route to alkylenedioxy-precocenes 10 having potential precocene antagonist activity - using the reaction of α, ω-dibromoalkanes with 6,7- or 7,8-dihydroxy-2,2-dimethyl-4-chromanones 4.5 is described. The structures of intermediate 4-chromanones 6-9 as well as the final regioisomer products 10 were determined by ^{1}H-NMR and MS methods

INTRODUCTION

Precocenes 1 and 2 isolated from natural sources (1) are known insect antijuvenile hormones (AJHs) (2) and nematocidal agents (3). Methylenedioxy-precocene 3 has been reported to be an antagonist to the oxidative activation of precocenes *in vivo* (4).



1 R = H
2 R = CH_3O



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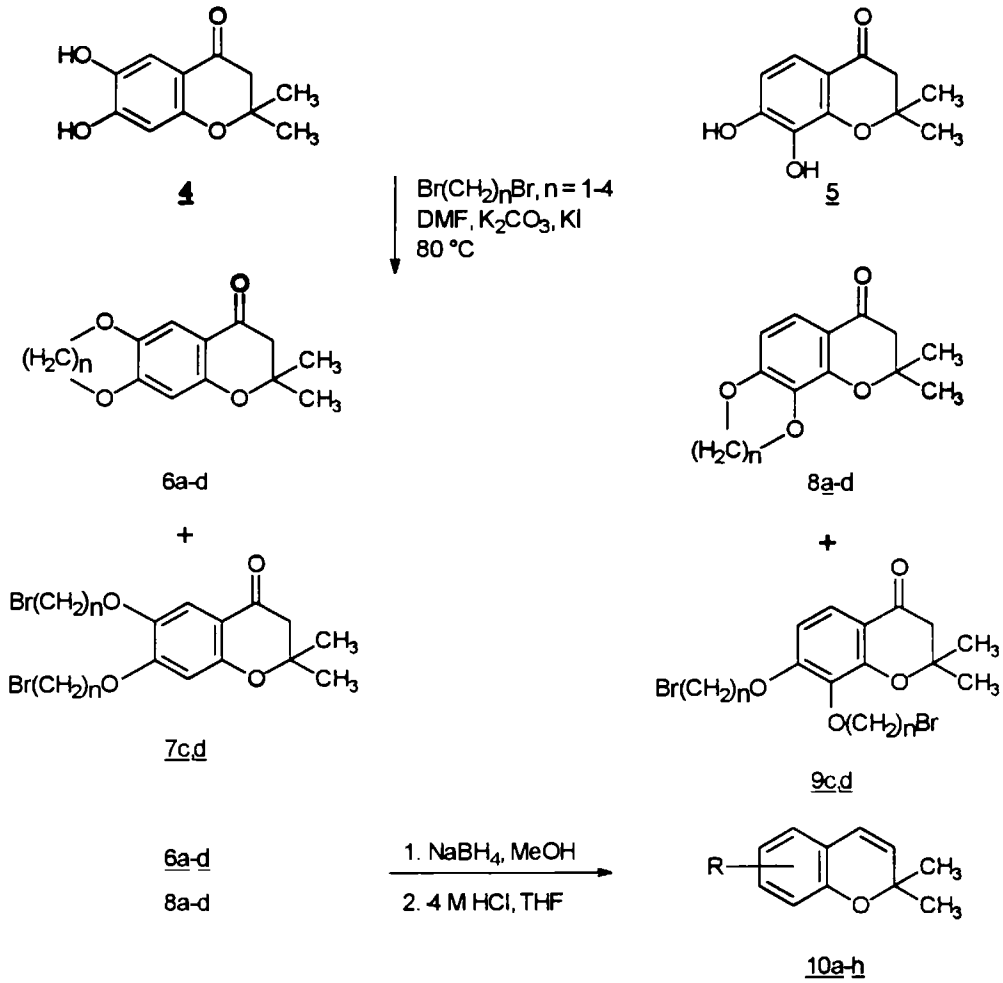
Recent works show that the main attention has been focused on syntheses of precocenes and their synthetic analogs of elevated AJH activity (5); however relatively few examples (6) can be found on the syntheses of precocene antagonists, such as 3 . In a view of our interest in the effects of synthetic precocenes on insect metamorphosis and reproduction (7) as well as on the development of nematodes (8) we needed to investigate the precocene antagonism of 3 , its analogs 10b-d and regioisomers 10e-h . Our aim is to learn more about the relationship between the alkylenedioxy-unit of the 2,2-dimethyl-2*H*-chromene system 10 and precocene antagonist activity. An evaluation of the methods described for the preparation of 6,7-methylenedioxy-2,2-dimethyl-2*H*-chromene 3 indicated that procedures often suffer from a long, tedious routes (9) with very low (2-16 %) overall yields (9,10), complicated reaction conditions and the use of expensive reagents (11). In order to circumvent these problems, we have developed a novel synthetic route for the preparation of alkylenedioxy-precocenes 10 .

RESULTS AND DISCUSSION

In this paper we describe a novel synthesis of title compounds using 6,7- and 7,8-dihydroxy-2,2-dimethyl-4-chromanones (12) 4 and 5 as readily available key intermediates.

The synthetic route (Scheme) to 10 is mainly based on the reaction of 6,7- and 7,8-dihydroxy-2,2-dimethyl-4-chromanones 4 and 5 with the corresponding α,ω-dibromoalkanes in the presence of potassium carbonate and potassium iodide in *N,N*-dimethylformamide at 80 °C using earlier observations concerning the methylenation of catechols (13).

Scheme



Accordingly, in the most dilute solution (at initial 4-chromanone concentration of 0.2 mol) the reactions of dihydroxy-4-chromanones 4 and 5 with dibromomethane and 1,2-dibromoethane were complete in several hours and the yields of 6,7- and 7,8-alkylenedioxy-2,2-dimethyl-4-chromanones 6a,b and 8a,b reached to 70%. However, when reacting these dihydroxy-4-chromanones 4 and 5 with 1,3-dibromopropane and 1,4-dibromobutane we detected two main products by TLC in the final reaction mixtures. After column chromatographic separation the structure of these products was determined by ^{1}H-NMR, MS methods and

microanalyses. The main products proved to be the 6,7- and 7,8-*bis*-(bromoalkyloxy)-2,2-dimethyl-4-chromanones 7c,d and 9c,d and the minors were the expected 6,7- and 7,8-alkylenedioxy-2,2-dimethyl-4-chromanones 6c,d and 8c,d . This observation can be rationalized by geometrical reasons *i.e.* the cyclization is less favourable in the case of seven and eight-membered systems. Further steps in the reaction sequence 6a-d and 8a-d → 10a-h followed reported procedures, *i.e.* sodium borohydride reduction and dehydration in hydrochloric acid (12,14).

In summary, the synthesis of products of general structure 10 has been accomplished *via* a novel pathway in 7-65 % overall yields from 6,7- and 7,8-dihydroxy-2,2-dimethyl-4-chromanones. Bioactivity studies of title compounds are under way and will be reported elsewhere.

EXPERIMENTAL

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. Analytical thin-layer chromatography was performed on precoated aluminium-backed 0.2 mm silica gel plates. Column chromatography was carried out with Kieselgel 60 silica gel using 3:1 hexane-ethyl acetate and 4:1 hexane-ether as eluents. ^{1}H-NMR spectra were determined for solutions in deuteriochloroform with TMS internal reference on a Varian Gemini-200 instrument. MS data were obtained on a VG TRIO-2 mass spectrometer in EI mode at 70 eV. Microanalyses were performed by Microlaboratory, L. Kossuth University, Debrecen, Hungary. Solvents were used either as purchased or dried and purified by standard methods.

General Procedure for the O-Alkylation of Dihydroxy-4-chromanones (4,5) – A stirred suspension of 4.2 g (20 mmol) of 4 or 5 , 8.3 g (60 mmol) of K_2CO_3, 0.5 g of KI in 100 mL DMF were added dropwise to a stirred solution of 30 mmol of the corresponding α,ω-dibromoalkane in 100 mL DMF at 80 °C. The reaction mixture was allowed to react at this temperature. When starting compounds were consumed (monitored by TLC), the inorganic solid material was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (200 mL) and washed with 5 % aqueous solution of NaOH (2×50 mL), water (2×100 mL), brine (2×100 mL) and dried over Na_2SO_4. The solvent was evaporated under vacuum and the residue thus obtained was either crystallised from EtOH or subjected to column chromatography using 3:1 hexane-ethyl acetate as the eluent. After column chromatographic separation of compounds 6c,d and 7c,d as well as 8c,d and 9c,d analytical samples were obtained by crystallisation from EtOH. Yields and spectral data are summarized in Table 1.

General Procedure for the Preparation of Alkylenedioxy-2H-chromenes (10a-h) – The corresponding 6,7- and 7,8-alkylenedioxy-4-chromanones 6a-d or 8a-d (10 mmol) were dissolved in methanol (25 mL) and stirred at room temperature until all the starting compounds were consumed (TLC monitoring). During this period $NaBH_4$ (1 g, 26 mmol) was added in portions to the reaction mixture. The solvent was removed under reduced pressure, and water (20 mL) was added to the residue. This mixture was extracted with CH_2Cl_2 (3×10 mL). The extract was washed with water (3×10 mL) and the solvent evaporated. The residue was then

dissolved in THF (15 mL) and treated with 4M HCl (20 mL) below 25 °C. When dehydration was complete (TLC) the reaction mixture was subsequently extracted with ether (3×10 mL) and the combined ethereal layers were washed with 2% aqueous NaOH solution (2×10 mL), water (3×10 mL) and brine (2×10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Analytical samples were obtained as oils by column chromatography using 4:1 hexane-ether as the eluent. Yields and spectral data are summarized in Table 2.

Table 1: Yields, Physical and Spectral Data of Compounds 6-9

Compound	Yield (%)	mp. (°C)	^{1}H-NMR δ (ppm), *J* (Hz)	MS *m/z* (%)
6a	68	59-60[a]	1.42 (6H, s), 2.62 (2H, s), 5.95 (2H, s), 6.36 (1H, s), 7.20 (1H, s)	220 (M^+, 46), 205 (100), 165 (98), 164 (67), 136 (15)
6b	72	118-120[b]	1.45 (6H, s), 2.66 (2H, s), 4.20-4.35 (4H, m), 6.41 (1H, s), 7.37 (1H, s)	234 (M^+, 44), 219 (100), 179 (68), 178 (60), 150 (10)
6c	9	84-85	1.43 (6H, s), 2.18 (2H, m), 2.66 (2H, s), 4.17 (2H, t, *J* = 6), 4.31 (2H, t, *J* = 6), 6.47 (1H, s), 7.46 (1H, s)	248 (M^+, 38), 233 (100), 193 (80), 192 (78), 164 (70)
6d	11	132-134	1.43 (6H, s), 2.06 (4H, m), 2.65 (2H, s), 3.50 (2H, m), 4.10 (2H, m), 6.37 (1H, s), 7.40 (1H, s)	262 (M^+, 56), 247 (100), 207 (30), 193 (45), 153 (50)
7c	59	69-71	1.45 (6H, s), 2.30-2.50 (4H, m), 2.66 (2H, s), 3.61 (4H, m), 4.12 (4H, m), 6.42 (1H, s), 7.32 (1H, s)	450 (M^+, 23), 435 (29), 394 (18), 123 (26), 69 (100)
7d	60	48-50	1.46 (6H, s), 2.06 (8H, m), 2.66 (2H, s), 3.52 (4H, m), 4.03 (4H, m), 6.36 (1H, s), 7.26 (1H, s)	478 (M^+, 8), 463 (5), 193 (10), 135 (67), 55 (100)
8a	56	118-120[c]	1.52 (6H, s), 2.75 (2H, s), 6.10 (2H, s), 6.55 (1H, d, *J* = 8), 7.55 (1H, d, *J* = 8)	220 (M^+, 42), 205 (52), 165 (70), 164 (100), 106 (20)
8b	74	152-154	1.50 (6H, s), 2.62 (2H, s), 4.25 (4H, s), 6.45 (1H, d, *J* = 8), 7.35 (1H, d, *J* = 8)	234 (M^+, 58), 219 (87), 179 (90), 178 (100), 94 (68)
8c	30	103-105	1.50 (6H, s), 2.27 (2H, m), 2.70 (2H, s), 4.30-4.40 (4H, m), 6.54 (1H, d, *J* = 8), 7.48 (1H, d, *J* = 8)	248 (M^+, 69), 233 (100), 193 (95), 192 (90), 164 (40)
8d	14	126-127	1.50 (6H, s), 1.85 (2H, m), 2.05 (2H, m), 2.70 (2H, s), 4.20 (2H, t, *J* = 6), 4.67 (2H, t, *J* = 6), 6.52 (1H, d, *J* = 8), 7.52 (1H, d, *J* = 8)	262 (M^+, 65), 247 (100), 207 (75), 193 (18), 152 (34)
9c	45	oil	1.50 (6H, s), 2.20-2.40 (4H, m), 2.70 (2H, s), 3.60-3.80 (4H, m), 4.05-4.30 (4H, m), 6.60 (1H, d, *J* = 8), 7.65 (1H, d, *J* = 8)	450 (M^+, 5), 435 (6), 217 (15), 151 (8), 121 (100)
9d	57	oil	1.50 (6H, s), 1.80-2.30 (8H, m), 2.70 (2H, s), 3.55 (4H, m), 4.05 (4H, m), 6.58 (1H, d, *J* = 8), 7.61 (1H, d, *J* = 8)	478 (M^+, 3), 398 (5), 247 (10), 152 (18), 135 (100)

[a] lit. mp. 61-62 °C (9), [b] lit. mp. 118-119 °C (15), [c] lit. mp. 119-120 °C (6)
The elemental analyses for C, H and Br were within ± 0.4 % of the theoretical values.

Table 2: Yields and Spectral Data of Compounds 10

10	Yield (%)	R	^{1}H-NMR δ (ppm), *J* (Hz)	MS *m/z* (%)
a	80	6,7-O-CH_2-O	1.40 (6H, s), 5.47 (1H, d, *J* = 10), 5.85 (2H, s), 6.17 (1H, d, *J* = 10), 6.35 (1H, s), 6.49 (1H, s)	204 (M^+, 19), 189 (100), 131 (8), 94 (10), 77 (8)
b	77	6,7-O-(CH_2)$_2$-O	1.37 (6H, s), 4.20 (4H, m), 5.52 (1H, d, *J* = 10), 6.25 (1H, d, *J* = 10), 6.32 (1H, s), 6.51 (1H, s)	218 (M^+, 19), 203 (100), 189 (11), 177 (4)
c	82	6,7-O-(CH_2)$_3$-O	1.40 (6H, s), 2.15 (2H, m), 4.10 (4H, m), 5.52 (1H, d, *J* = 10), 6.20 (1H, d, *J* = 10), 6.43 (1H, s), 6.62 (1H, s)	232 (M^+, 22), 217 (100), 189 (16), 91 (18)
d	79	6,7-O-(CH_2)$_4$-O	1.41 (6H, s), 2.05 (4H, m), 3.58 (2H, m), 3.95 (2H, m), 5.50 (1H, d, *J* = 10), 6.22 (1H, d, *J* = 10), 6.40 (1H, s), 6.63 (1H, s)	246 (M^+, 38), 231 (100), 189 (19), 177 (8), 91 (22)
e	83	7,8-O-CH_2-O	1.50 (6H, s), 5.51 (1H, d, *J* = 10), 5.95 (2H, s), 6.27 (1H, d, *J* – 10), 6.38 (1H, d, *J* = 8), 6.56 (1H, d, *J* = 8)	204 (M^+, 20), 189 (100), 159 (30), 94 (18), 77 (20)
f	88[a]	7,8-O-(CH_2)$_2$-O	1.50 (6H, s), 4.27 (4H, m), 5.50 (1H, d, *J* = 10), 6.25 (1H, d, *J* = 10), 6.40 (1H, d, *J* = 8), 6.51 (1H, d, *J* = 8)	218 (M^+, 21), 203 (100), 147 (10), 91 (25)
g	76[b]	7,8-O-(CH_2)$_3$-O	1.47 (6H, s), 2.20 (2H, m), 4.25 (4H, m), 5.52 (1H, d, *J* = 10), 6.25 (1H, d, *J* = 10), 6.47 (1H, d, *J* = 8), 6.55 (1H, d, *J* = 8)	232 (M^+, 70), 217 (100), 189 (19), 176 (17), 91 (18)
h	85	7,8-O-(CH_2)$_4$-O	1.45 (6H, s), 1.90 (4H, m), 4.20 (2H, m), 4.40 (2H, m), 5.50 (1H, d, *J* = 10), 6.25 (1H, d, *J* = 10), 6.45 (1H, d, *J* = 8), 6.60 (1H, d, *J* = 8)	246 (M^+, 35), 231 (100), 189 (15), 177 (49), 176 (18), 91 (18)

[a] solidified on standing: mp. 67-69 °C, [b] solidified on standing: mp. 91-93 °C

The elemental analyses for C and H were within ± 0.4 % of the theoretical values.

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