SYNTHESIS OF NEW BISCHROMENES: CHEMICAL PROBES FOR PRECOCENE RECEPTORS

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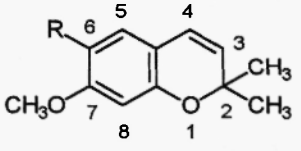
Abstract : Synthesis of new bischromenes (5-10) - possessing potential insect antijuvenile hormone activity - using the reaction of α,ω-dibromoalkanes with hydroxy-2,2-dimethyl-4-chromanones (1a-e) is described. The structures of new intermediate bis-4-chromanones (2-4) as well as the target bis-2*H*-chromenes (5-10) were determined by ^{1}H-NMR and MS methods.

INTRODUCTION

Precocene 1 and 2 are naturally occuring chromonoids (1) possessing insect antijuvenile hormone activity (2). A considerable effort has been made to elucidate the mode of action of these compounds and details of the chemical structure essential for this unique bioactivity (3) in order to produce synthetic precocenes of more pronounced activity.



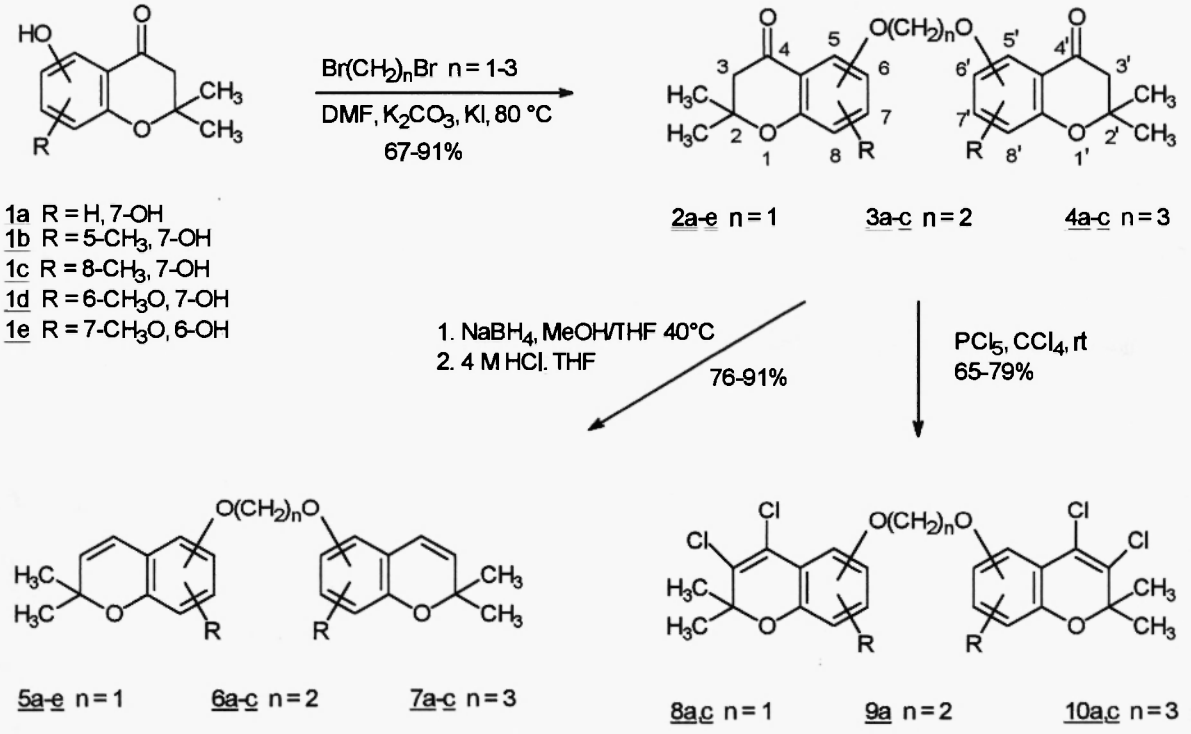
R = H Precocene-1
R = CH_3O Precocene-2

For these purposes hundreds of analogs of natural precocenes have been synthesized (4) and as a result of these extensive chemical and biological investigations the mechanism by which precocenes exert their action is now partly understood (5). It is well established that the precocenes are selectively activated by specific enzymes in the insect *corpus allatum*, and that these biotransformation products then alkylate important cellural components causing death and destruction of the allatal cells (6). During the structure-activity relationship studies relatively few attention has been focused on geometrical requirements of whole precocene molecule, that must also be of importance for optimal bioactivity (7). To learn the extent to which the geometrical requirements needed for elevated insect antijuvenile hormone activity and gain some information about precocene receptor(s) we decided to synthesize a series of new bis-2*H*-chromenes (5-10) thereby changing considerably the environment of C-7 position, as well as the shape and size of the whole precocene molecule, particularly in the case of the synthesis of these bis-2*H*-chromenes linked by spacers of different length.

RESULTS AND DISCUSSION

In this paper we describe the synthesis of title compounds from hydroxy-2,2-dimethyl-4-chromanones (1a-e) as readily available key intermediates (8). The synthetic route (Scheme) to (5-10) is based on the reaction of hydroxy-2,2-dimethyl-4-chromanones (1a-e) with the appropriate α,ω-dibromoalkanes in the presence of potassium carbonate and potassium iodide at 80 °C.

Scheme



Thus, the reactions of hydroxy-2,2-dimethyl-4-chromanones (1a-e) with α,ω-dibromoalkanes were complete in 10 to 20 hours and the yields of the intermediate bis-4-chromanones (2-4) reached to 67-91 %. The structure of these new compounds was determined by ^{1}H-NMR and MS methods. Sodium borohydride reduction of bis-4-chromanones (2-4) in MeOH/THF followed by dehydration in 4M HCl/THF furnished the corresponding new bischromenes (5-7) in 76-91% yields. The reactions of bis-4-chromanones (2-4) with four equivalent of PCl_5 in CCl_4 at room temperature (9) afforded the new bis-3,4-dichloro-2H-chromenes (8-10) in 65-79% yields.

In summary, the synthesis of target compounds of general structure (5-10) has been accomplished *via* two alternative reaction sequence in good overall yields. The *in vitro* and *in vivo* bioactivity studies of title compounds are in progress and the results of these investigations will be reported in a separate paper.

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 Preparation of bis(2,2-dimethyl-4-chromanone-7-oxy)alkanes (2-4). – A stirred suspension of 19.2 g (100 mmol) of (1a), 15 g (108 mmol) of K_2CO_3, 0.5 g of KI, 55 mmol of the corresponding α,ω-dibromoalkane in 150 mL DMF were allowed to react at 80 °C. When starting compound was 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 crystallised from EtOH or MeOH. Yields and spectral data are summarized in Table 1.

General Procedure for the Preparation of bis(2,2-dimethyl-2H-chromen-7-oxy)alkanes (5-7). – The corresponding bis-4-chromanones (2-4) (50 mmol) were dissolved in MeOH/THF (250/120 mL) and stirred at 40 °C until all the starting compounds were consumed (TLC monitoring). During this period $NaBH_4$ (10 g, 260 mmol) was added in portions to the reaction mixture. The solvent was removed under reduced pressure, and water (200 mL) was added to the residue. This mixture was extracted with CH_2Cl_2 (3×100 mL). The extract was washed with water (3×100 mL) and the solvent evaporated. The residue was then dissolved in THF (200 mL) and treated with 4M HCl (250 mL) below 25 °C. When dehydration was complete (TLC) the reaction mixture was subsequently extracted with ether (3×100 mL) and the combined ethereal layers were washed with 2% aqueous NaOH solution (2×100 mL), water (3×100 mL) and brine (2×100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Analytical samples were obtained by crystallisation from MeOH or by column chromatography using 4:1 hexane-ether as the eluent. Yields and spectral data are summarized in Table 2.

General Procedure for the Preparation of bis(2,2-dimethyl-3,4-dichloro-2H-chromen-7-oxy)alkanes (8-10). – A stirred suspension of the corresponding bis-4-chromanone (2-4) (20 mmol) and 17g (82 mmol) of PCl_5 in CCl_4 (200 mL) was allowed to react at room temperature. When starting compound was consumed (monitored by TLC), 200 mL of water was added and the mixture was stirred for 30 minutes.. The layers were separated, the organic layer was washed with 5 % aqueous solution of NaOH (2×100 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 crystallised from EtOH. Yields and spectral data are summarized in Table 2.

Table 1. Yields, Physical and Spectral Data of Compounds 2-4

Com-pound	Yield (%)	mp. (°C)	^{1}H-NMR δ (ppm), *J* (Hz)	MS *m/z* (%)
2a	82	71-72	1.47 (12H, s), 2.65 (4H, s), 5.75 (2H, s), 6.62 (2H, d, J_1=2), 6.70 (2H,dd, J_1=2, J_2=10), 7.80 (2H, d, J_2=10)	396 (M^+, 55), 205 (100)
2b	79	153-154	1.45 (12H, s), 2.61 (6H, s), 2.66 (4H, s), 5.71 (2H, s), 6.43 (2H, d, *J*=2), 6.48 (2H, d, *J*=2)	424 (M^+, 36), 268 (100)
2c	85	188-189	1.45 (12H, s), 2.07 (6H, s), 2.67 (4H, s), 5.85 (2H, s), 6.87 (2H, d, *J*=10), 7.75 (2H, d, *J*=10)	424 (M^+, 34), 163 (100)
2d	79	216-218	1.45 (12H, s), 2.67 (4H, s), 3.87 (6H, s), 5.82 (2H, s), 6.85 (2H, s), 7.30 (2H, s)	456 (M^+, 22), 235 (100)
2e	87	150-152	1.47 (12H, s), 2.65 (4H, s), 3.90 (6H, s), 5.75 (2H, s), 6.45 (2H, s), 7.65 (2H, s)	456 (M^+, 19), 235 (100)
3a	67	165-167	1.46 (12H, s), 2.68 (4H, s), 4.35 (4H, s), 6.42 (2H, d, J_1=2), 6.57 (2H,dd, J_1=2, J_2=10), 7.80 (2H, d, J_2=10)	410 (M^+, 7), 203 (100)
3b	69	157-159	1.45 (12H, s), 2.61 (6H, s), 2.68 (4H, s), 4.31 (4H, s), 6.28 (2H, m), 6.35 (2H, m)	438 (M^+, 20), 349 (100)
3c	63	200-202	1.47 (12H, s), 2.08 (6H, s), 2.67 (4H, s), 4.41 (4H, s), 6.58 (2H, d, *J*=10), 7.74 (2H, d, *J*=10)	438 (M^+, 74), 177 (100)
4a	83	153-155	1.46 (12H, s), 2.30 (2H, m), 2.65 (4H, s), 4.17 (4H, t, *J*=5), 6.37 (2H, d, J_1=2), 6.55 (2H,dd, J_1=2, J_2=10), 7.80 (2H, d, J_2=10)	424 (M^+, 16), 217 (100)
4b	84	135-137	1.43 (12H, s), 2.26 (2H, m), 2.60 (6H, s), 2.66 (4H, s), 4.15 (4H, t, *J*=5), 6.28 (2H, m), 6.33 (2H, m)	452 (M^+, 5), 191 (100)
4c	91	172-174	1.46 (12H, s), 2.07 (6H, s), 2.35 (2H, m), 2.67 (4H, s), 4.25 (4H, t, *J*=5), 6.58 (2H, d, *J*=10), 7.75 (2H, d, *J*=10)	452 (M^+, 54), 191 (100)

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

Table 2. Yields and Spectral Data of Compounds 5-10

Compound	Yield (%)	mp. (°C)	^{1}H-NMR δ (ppm), *J* (Hz)	MS *m/z* (%)
5a	79	79-81	1.40 (12H, s), 5.47 (2H, d, *J*=10), 5.62 (2H, s), 6.25 (2H, d, *J*=10), 6.56 (4H, m), 6.85 (2H,d, *J*=10),	378 (M^+, 27), 349 (100)
5b	91	85-86	1.40 (12H, s), 2.24 (6H, s), 5.50 (2H, d, *J*=10), 5.60 (2H, s), 6.40 (2H, m)	392 (M^+, 15), 378 (100)
5c	77	86-88	1.41 (12H, s), 2.05 (6H, s), 5.50 (2H, d, *J*=10), 5.70 (2H, s), 6.26 (2H, d, *J*=10), 6.70 (2H, d, *J*=8), 6.76 (2H, d, *J*=8)	392 (M^+, 29), 377? (100)
5d	68	oil	1.42 (12H, s), 3.80 (6H, s), 5.53 (2H, d, *J*=10), 5.70 (2H, s), 6.25 (2H, d, *J*=10), 6.56 (2H, s), 6.80 (2H, s)	424 (M^+, 65), 409 (100)
5e	82	oil	1.40 (12H, s), 3.80 (6H, s), 5.47 (2H, d, *J*=10), 5.57 (2H, s), 6.22 (2H, d, *J*=10), 6.40 (2H, s), 6.92 (2H, s)	424 (M^+, 62), 409 (100)
6a	76	78-80	1.43 (12H, s), 4.23 (4H, s), 5.45 (2H, d, *J*=10), 6.25 (2H, d, *J*=10), 6.43 (4H, m), 6.85 (2H,d, *J*=10)	378 (M^+, 27), 364? (100)
6b	82	115-117	1.43 (12H, s), 2.25 (6H,s), 4.23 (4H, s), 5.50 (2H, d, *J*=10), 6.25 (2H, m), 6.30 (2H, m), 6.45 (2H, d, *J*=10)	406 (M^+, 23), 391 (100)
6c	81	119-121	1.43 (12H,s), 2.07 (6H, s), 4.30 (4H, s), 5.50 (2H, d, *J*=10), 6.28 (2H, d, *J*=10), 6.45 (2H, d, *J*=8), 6.80 (2H, d, *J*=8)	406 (M^+, 9), 391 (100)
7a	81	65-67	1.40 (12H, s), 2.17 (2H, m), 4.05 (4H, t, *J*=5), 5.42 (2H, d, *J*=10), 6.25 (2H, d, *J*=10), 6.37 (2H, m), 6.84 (2H,d, *J*=10)	392 (M^+, 28), 378? (100)
7b	78	78-80	1.40 (12H, s), 2.18 (2H, m), 2.25 (6H, s), 4.08 (4H, t, *J*=5), 5.50 (2H, d, *J*=10), 6.25 (4H, m), 6.45 (2H, d, *J*=10)	420 (M^+, 11), 405 (100)
7c	78	96-98	1.41 (12H, s), 2.07 (6H, s), 2.27 (2H, m), 4.15 (4H, t, *J*=5), 5.49 (2H, d, *J*=10), 6.27 (2H, d, *J*=10), 6.39 (2H, d, *J*=8),	420 (M^+, 27), 405 (100)
8a	73	77-78	1.57 (12H, s), 5.67 (2H, s), 6.60 (2H, d, J_1=2), 6.69 (2H, dd, J_1=2, J_2=10), 7.32 (2H, d, J_2=10)	502 (M^+, 11), 149 (100)
8c	69	37-39	1.55 (12H, s), 2.05 (6H, s), 5.77 (2H, s), 6.82 (2H, d, *J*=10), 7.25 (2H, d, *J*=10)	530 (M^+, 42), 271 (100)
9a	79	185-187	1.55 (12H, s), 4.30 (4H, s), 6.45 (2H, d, J_1=2), 6.58 (2H, dd, J_1=2, J_2=10), 7.35 (2H, d, J_2=10)	516 (M^+, 7), 282 (100)
10a	65	71-73	1.54 (12H, s), 2.25 (2H, m), 4.12 (4H, t, *J*=5), 6.42 (2H, d, J_1=2), 6.52 (2H,dd, J_1=2, J_2=10), 7.32 (2H, d, J_2=10)	530 (M^+, 12), ? (100)
10c	71	oil	1.55 (12H, s), 2.05 (6H, s), 2.30 (2H, m), 4.17 (4H, t, *J*=5), 6.50 (2H, d, *J*=10), 7.20 (2H, d, *J*=10)	558 (M^+, 21), 280 (100)

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

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support from Alkaloida Chemical Company Ltd. (Tiszavasvári, Hungary). Our thank is also due to Mrs. Fazekas Lajos, Mrs. Kovách Álmos and Csáki Erika for their technical assistance.

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Received April 15, 1995