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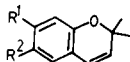
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Preparation of potential insect antijuvenile hormone agents with 15-crown-5 and 18-crown-6 moieties connecting the C-6 and C-7 positions of the 2 *H*-chromene ring of precocenes is described.

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Recently, the incorporation of ionophoric groups in bioactive molecules to modify the corresponding pharmacokinetic properties has been adopted in drug design. Among the possible ionophoric groups to be considered for this aim, crown ethers have deserved a special attention (1).

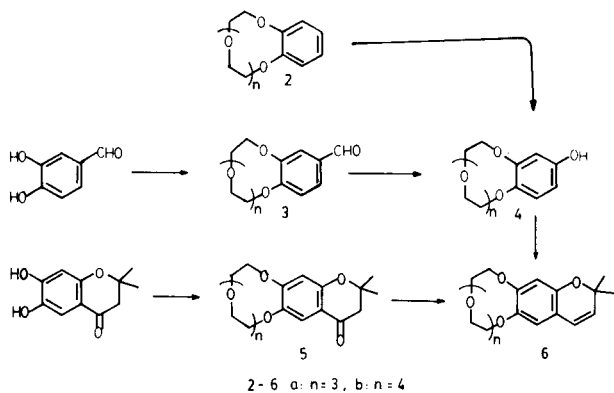
Our continuing interest in developing potential insect antijuvenile hormone agents has led us to the synthesis of several precocene analogs (2). In this context, we anticipated that analogs with a built-in crown ether moiety bridging the C-6 and C-7 positions of the 2 *H*-chromene ring of precocenes could exhibit interesting properties as far as absorption and transport is concerned.



Precocene I, $R^1 = OCH_3$, $R^2 = H$

Precocene II, $R^1 = R^2 = OCH_3$

In the present communication, we describe the preparation of 15-crown-5 and 18-crown-6 precocene analogs **5** ($n = 3, 4$) brought about as depicted in the scheme.



The attempted hydroxylation of the benzene ring of easily available benzocrown ethers **2** by a sequence implying Friedel-Crafts acetylation followed by Baeyer-Villiger oxidation and hydrolysis proved to be unpractical, due to deactivation of the aluminium chloride, used as catalyst in the first step, by formation of a stable crown ether adduct (3). Recently, this difficulty has been overcome by Wada *et al.* (4) carrying out the reaction with acetic anhydride-

polyphosphoric acid in acetic acid.

Alternatively, the second route started from 4'-formylbenzocrown ethers **3**, prepared, in higher yields (**3a**, 40%; **3b**, 57%) than by application of the conventional procedure (5), by reaction of 3,4-dihydroxybenzaldehyde with tetra- or pentaethyleneglycol ditosylates in acetonitrile in the presence of excess of cesium fluoride, which plays a dual role as base and cyclization template (6). Treatment of **3** with diethyl ether saturated with hydrochloric acid afforded the corresponding 4'-hydroxybenzocrown ethers **4** (**4a**, 44%; **4b**, 43%). However, condensation of **4** with 3-methyl-2-butenal in the presence of titanium(IV) ethoxide gave poor yields of the desired crown precocenes **6** (**6a**, 16%; **6b**, 5%). Other methods of chromenylation attempted were unsuccessful.

Finally, bridging of the 6 and 7 positions of 6,7-dihydroxy-2,2-dimethyl-4-chromanone (**8**) was accomplished by the above cesium fluoride procedure to give, after the usual work up and purification by column chromatography on silica gel eluting with 98:2 chloroform:methanol, excellent yields of the corresponding crown ether 4-chromanones **5** (**5a**, 50%; **5b**, 85%).

Lithium aluminium hydride reduction of these compounds in refluxing diethyl ether afforded directly good yields of the corresponding crown ether chromenes **6**, isolated as thick colorless oils (**6a**, 48%; **6b**, 53%).

Results of the biological activity will be published elsewhere.

EXPERIMENTAL

The following instruments were used for the spectra described. Perkin-Elmer 257 (ir), Perkin-Elmer R12B with tetramethylsilane as internal standard (¹H-nmr) and AEI MS 902S (mass spectrum). Microanalyses were performed with Carlo Erba CHN Microanalyzer Model 1106.

2,3-(4'-Hydroxybenzo)-1,4,7,10,13-pentaoxacyclopentadeca-2-ene (**4a**).

A solution of *m*-chloroperoxybenzoic acid (2.10 g, 0.0135 mole) in methylene chloride (30 ml) was added dropwise to a vigorously stirred solution of **3a** (2.01 g, 0.0068 mole) in methylene chloride (30 ml) at 0° under a dry nitrogen atmosphere. The mixture was stirred for 16 hours at room temperature and was concentrated at reduced pressure in a rotary evaporator. The residue was diluted with dry diethyl ether (30 ml) and concentrated hydrochloric acid (0.5 ml) was added. The mixture was stirred for 3 hours at room temperature, the crude product was concentrated at reduced pressure in a rotary evaporator to give a residue which was purified by chromatography on a 15 cm × 1.5 cm silica gel column (20 g, 1:9 methanol:chloroform) to yield **4a** (0.85 g, 44%) as a colorless thick

oil; ir (chloroform): 3400-3100, 2995, 2910, 2885, 1605, 1510, 1450, 1360, 1345, 1290, 1240, 1170, 1140, 1125, 1110, 1060 cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 6.72 (1H, *H-Ar*, d, $J = 8$ Hz), 6.45 (1H, *H-Ar*, d, $J = 8$ Hz), 6.5 (1H, *H-Ar*, m), 4.3-3.4 (16H, $-\text{OCH}_2\text{CH}_2\text{O}-$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_6$: C, 55.62; H, 7.33. Found: C, 55.36; H, 7.17.

6,7-(1',4',7',10',13'-Pentaoxatridecandiyl)-2,2-dimethylchroman-4-one (5a).

A solution of tetraethyleneglycol ditosylate (0.502 g, 0.001 mole) in dry acetonitrile (20 ml) was added dropwise to a stirred solution of 6,7-dihydroxy-2,2-dimethylchroman-4-one (0.208 g, 0.001 mole) and cesium fluoride (1.25 g, 0.005 mole) in dry acetonitrile (10 ml) under a dry nitrogen atmosphere. The mixture was stirred under reflux for 24 hours allowed to cool to room temperature and filtered. The filtrate was dissolved in chloroform and extracted with sodium hydroxide (10%), the organic layer was washed with saturated aqueous sodium chloride solution and dried (magnesium sulfate). The residue was purified by chromatography on a 15 cm \times 1.5 cm silica gel column (10 g, 98:2 chloroform:methanol) to yield 5a (0.18 g, 50%); mp 106° (heptane; ir (chloroform): 2980, 2930, 2870, 1675, 1615, 1590, 1500, 1445, 1395, 1375, 1360, 1320, 1280, 1240, 1185, 1170, 1140, 1110, 1060 cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 7.2 (1H, *H-Ar*, s), 6.3 (1H, *H-Ar*, s), 4.2-3.6 (16H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 2.7 (2H, CH_2CO , s), 1.4 (6H, CH_3 , s); ms: m/e 367 ($M+1$), 366 (M^+), 351 ($M-\text{CH}_3$), 263 ($M-\text{C}_5\text{H}_{11}\text{O}_3$), 220 ($M-\text{C}_7\text{H}_{13}\text{O}_3$), 219 ($M-\text{C}_9\text{H}_{15}\text{O}_3$), 179 ($M-\text{C}_{10}\text{H}_{19}\text{O}_3$), 178 ($M-\text{C}_{11}\text{H}_{23}\text{O}_3$), 150 ($M-\text{C}_{11}\text{H}_{23}\text{O}_4$).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_7$: C, 62.28; H, 7.15. Found: C, 62.03; H, 7.16.

6,7-(1',4',7',10',13',16'-Hexaoxahexadecandiyl)-2,2-dimethylchroman-4-one (5b).

Application of the same procedure described above, using pentaethyleneglycol ditosylate (1.41 g, 0.002 mole), 6,7-dihydroxy-2,2-dimethylchroman-4-one (0.446 g, 0.002 mole), cesium fluoride (2.76 g, 0.01 mole) and dry acetonitrile (40 ml), afforded 5b (0.695 g, 85%) mp 69° (heptane); ir (chloroform): 2980, 2930, 2870, 1675, 1610, 1580, 1500, 1440, 1370, 1355, 1320, 1275, 1240, 1200, 1180, 1160, 1130, 1110, 1060 cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 7.4 (1H, *H-Ar*, s), 6.5 (1H, *H-Ar*, s), 4.4-3.6 (20H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 2.7 (2H, CH_2CO , s), 1.5 (6H, CH_3 , s); ms: m/e 411 ($M+1$), 410 (M^+), 395 ($M-\text{CH}_3$), 307 ($M-\text{C}_5\text{H}_{11}\text{O}_3$), 263 ($M-\text{C}_7\text{H}_{15}\text{O}_3$), 220 ($M-\text{C}_9\text{H}_{19}\text{O}_3$), 219 ($M-\text{C}_9\text{H}_{19}\text{O}_4$), 194 ($M-\text{C}_{11}\text{H}_{23}\text{O}_4$), 179 ($M-\text{C}_{12}\text{H}_{25}\text{O}_4$), 178 ($M-\text{C}_{12}\text{H}_{25}\text{O}_4$).

Anal. Calcd. for $\text{C}_{23}\text{H}_{30}\text{O}_8$: C, 61.45; H, 7.37; Found: C, 61.69; H, 7.40.

6,7-(1',4',7',10',13'-Pentaoxatridecandiyl)-2,2-dimethyl-2H-chromene (6a).

a) From 4a.

A solution of 4a (1.4 g, 0.005 mole) in dry toluene (3 ml) was added dropwise to a stirred solution of titanium(IV) ethoxide (0.280 g, 0.012 mole) in dry toluene (3 ml) at room temperature under a dry nitrogen atmosphere. The mixture was refluxed for 30 minutes, ethanol was distilled off and the mixture was allowed to cool to room temperature. A solution of 4-methylbut-2-enal (0.619 g, 0.0074 mole) in dry toluene (10 ml) was added dropwise and the volume was adjusted with toluene (30 ml). Then, the mixture was refluxed with stirring for 8 hours, cooled to room

temperature and evaporated to give a residue. Purification of this residue by chromatography on 40 cm \times 2 cm aluminium oxide column (50 g, 1:1 benzene:ethyl acetate) yielded 6a (0.272 g, 16%) as a thick colorless oil; ir (chloroform): 2980, 2930, 2880, 1620, 1505, 1460, 1430, 1365, 1280, 1255, 1220, 1185, 1140, 1110, 1060 cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 6.43 (1H, *H-Ar*, s), 6.24 (1H, *H-Ar*, s), 6.1 (1H, $\text{H-C}=\text{C}$, d, $J = 10$ Hz), 5.3 (1H, $\text{H-C}=\text{C}$, d, $J = 10$ Hz), 4.1-3.6 (16H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 1.35 (6H, CH_3 , s).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_6$: C, 65.13; H, 7.48. Found: C, 64.73; H, 7.53.

b) From 5a.

Lithium aluminium hydride (0.056 g, 0.0015 mole) was added to a stirred solution of 5a (0.535 g, 0.0015 mole) in dry diethyl ether (30 ml). The mixture was stirred for two hours at room temperature and excess hydride was destroyed by adding ethyl acetate dropwise. The precipitate was removed by filtration and the filtrate evaporated to give the corresponding chromanol (0.210 g); $^1\text{H-nmr}$ (deuteriochloroform): δ 7.33 (1H, *H-Ar*, s), 6.45 (1H, *H-Ar*, s), 4.3-3.5 (17H, H-C-O), 2.65 (1H, CH_2 , s), 2.55 (1H, CH_2 , d, $J = 9$ Hz), 1.45 (6H, CH_3 , s). This product was dissolved in chloroform, allowed to stand at room temperature for one hour and then evaporated at reduced pressure to afford 6a as a thick colorless oil (0.240 g, 48%).

6,7-(1',4',7',10',13',16'-Hexaoxahexadecandiyl)-2,2-dimethyl-2H-chromene (6b).

Application of the same procedure described above using lithium aluminium hydride (0.038 g, 0.001 mole), and 5b (0.392 g, 0.00094 mole) in dry diethyl ether afforded 6b (0.197 g, 53%) as a thick colorless oil; ir (chloroform): 3000, 2970, 2920, 2880, 1615, 1500, 1455, 1435, 1360, 1280, 1260, 1175, 1130, 1060, cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 6.55 (1H, *H-Ar*, s), 6.35 (1H, *H-Ar*, s), 6.1 (1H, $\text{H-C}=\text{C}$, d, $J = 10$ Hz), 5.43 (1H, $\text{H-C}=\text{C}$, d, $J = 10$ Hz), 4.2-3.5 (20H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 1.4 (6H, CH_3 , s).

Anal. Calcd. for $\text{C}_{23}\text{H}_{30}\text{O}_8$: C, 63.94; H, 7.96. Found: C, 63.68; H, 7.96.

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