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The oligomerization and acylation of precocene I

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The oligomerization of precocene I with Brönsted and Lewis acids has been studied. In this way, the reaction of this chromene with HCl/MeOH gave two dimers, a trimer, a linear tetramer and a mixture of pentamers, whilst with $FeCl_3$/HOAc a dimer and six cyclic tetramers were obtained. The cyclization of linear tetramers occurs between C-4‴ and C-6 or, in lower yield, between C-4‴ and C-8. In the formation of linear tetramers the C-8 functionalization was not detected, which could indicate that it occurs during the cyclization process. Moreover, oxidative one-electron coupling reactions were also observed in the treatment of precocene I with $FeCl_3$/HOAc. On the other hand, the reaction of precocene I with $FeCl_3/Ac_2O$ produced 6-acylation leading to the natural chromene encecalin.

1. Introduction

The chromenes precocene I (**1**) and precocene II (**2**), isolated from *Ageratum houstonianum*, have been shown to induce precocious metamorphosis when applied to larval stages of insects.[1–3] Analogues of these antijuvenile hormones have been synthesized with the aim of obtaining compounds with better activity.[4–8] In this way, we have prepared dimers A (**4**), C (**6**) and D (**7**) by treatment of precocene II (**2**) with $SiO_2/AgNO_3$.[9,10] We also obtained the 3,3′-dimer of precocene II (**8**) in one step by treatment of **2** with dry ferric trichloride in acetic acid.[11] Whilst **4** and **7** were obtained by acid dimerization, the formation of dimers **6** and **8** occurred by oxidative one-electron coupling reactions. We also studied the reaction of precocene II (**2**) with $FeCl_3$ in Ac_2O leading to the trimer **9** and to the 3-acylated precocene II.[12] Later, other authors also obtained this trimer **9** by treatment of **2** with $AlCl_3$ in diethyl ether.[13]

Continuing with these studies we describe here the results obtained in the reactions of precocene I (**1**) with HCl/MeOH, Fe_3Cl/HOAc and Fe_3Cl/Ac_2O, comparing them with those obtained in the reactions of precocene II (**2**) with these acids.

2. Results and discussion

The reaction of precocene I (**1**) with HCl/MeOH afforded the dimers **3** and **10**, the trimer **11**, the tetramer **12** and a mixture of pentamers. The structure of the dimer **3** was given on the basis of the following considerations: In the mass spectrum the molecular ion was in accordance with the molecular formula $C_{24}H_{28}O_4$ showing also significant peaks at m/z 191 and 189, characteristic of the monomeric fragments produced by the cleavage of the 3′,4-bond. The ^1H NMR spectrum showed signals of four methyls, two methoxy groups, two H-3 at δ_H 1.79 (t, J=12.5 Hz) and 2.01 (dd, J=12.5, 6.0 Hz), H-4 at δ_H 3.52 (dd, J=12.5, 6.0 Hz), H-4′ at δ_H 6.00 (br s) and four aromatic hydrogens. These signals and the ^{13}C NMR spectrum (Table 2) were assigned using double resonance, COSY,

Table 1
^{13}C NMR data of **1**, **5** and **19**

Carbon	1	5	19
2	76.2	76.6	77.6
3	127.8	48.9	127.0
4	121.9	71.7	121.3
5	126.9	130.5	128.2
6	106.6	108.4	120.6
7	160.6	160.4	161.0
8	102.0	101.7	99.5
9	114.6	115.0	113.9
10	154.2	154.6	158.4
11	28.0	27.8[a]	28.3
12	28.0	24.8[a]	28.3
13	55.3	55.2	55.5
14			197.6
15			30.1

[a] These values can be interchanged.

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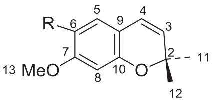
Table 2
^{13}C NMR data of dimers **3** and **10**

Carbon	3	10	Carbon	3	10
2	74.6	75.1	2′	78.1	76.2
3	45.4	41.7	3′	143.1	127.4
4	37.3	30.3	4′	120.9	121.9
5	130.1	130.0	5′	126.4	126.6
6	107.3	106.9	6′	106.6	125.1
7	159.4	158.9	7′	160.4	158.2
8	101.6	101.4	8′	101.6	99.3
9	116.0	117.1	9′	114.6	114.1
10	155.5	155.0	10′	153.8	152.3
11	29.2	29.8	11′	26.8[b]	27.9[c]
12	24.0	24.2	12′	27.2[b]	28.1[c]
13	55.1[a]	55.5	13′	55.2[a]	55.1

[a–c]These values can be interchanged.

HMQC and HMBC experiments. This compound possesses an analogous structure to that of **4**, which was obtained under the same conditions with precocene II (**2**).[14]



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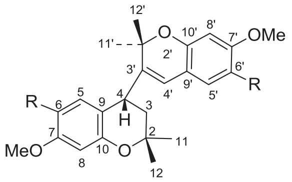
2 R = OMe



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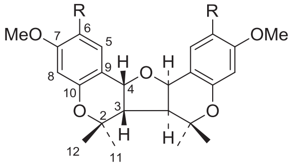
4 R = OMe



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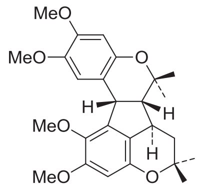
6 R = OMe



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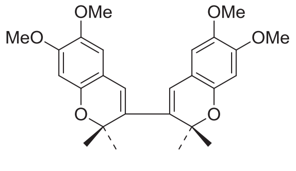

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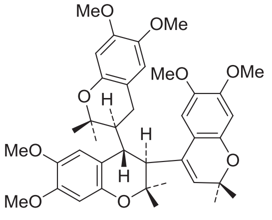

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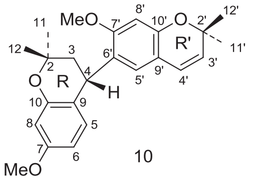
The second of the dimers (**10**) is isomeric with **3**, but its structure presents now the union of the two monomeric units between C-4 and C-6′. This dimer can be formed by protonation of the 3,4-double bond of precocene I (**1**) to form a carbocation at C-4, which attacks a second molecule of **1** at C-6′, with aromatic substitution. This compound had been prepared by treatment of precocene I with trichloroacetic acid-silica gel.[15,16] We have now unambiguously assigned its ^{1}H and ^{13}C NMR spectra using bidimensional NMR data.

The protonation of the dimer **10** with formation of a 4′-carbocation and attack on the C-6″ of a third molecule of precocene I (**1**) forms the trimer **11**, which has the molecular formula $C_{36}H_{42}O_6$ (m/z 570.2975). Its ^{1}H NMR spectrum showed six methyls, three methoxy groups, H-3 at δ_H 1.67 (m) and 1.92 (dd), H-3′ at δ_H 1.67 (m) and 1.97 (dd), H-4 and H-4′ at δ_H 4.39 (br s) and 4.33 (br s), respectively, whilst H-3″ and H-4″ resonate at δ_H 5.40 and 6.09 as two doublets (J=10.0 Hz). Signals also appear in this spectrum of seven aromatic protons, H-5, H-6 and H-8 at δ_H 6.57 (d, J=8.0 Hz), 6.22 (dd, J=8.0, 2.0 Hz) and 6.24 (br s), respectively, whilst H-5″, H-8″, H-5′ and H-8′ resonate as singlets at δ_H 6.44, 6.26, 6.46 and 6.39, respectively. These signals and the ^{13}C NMR spectrum of **11** (Table 3) were assigned by a study of their COSY, HSQC and HMBC spectra. Indeed the resonances of the geminal methyl group at C-2 and the 3α,3β-hydrogens could be located by running a NOESY experiment. This compound had been identified by other authors as a component of an unresolved mixture, which had been obtained by treatment of precocene I with trichloroacetic acid–silica gel.[16]

To another product obtained in this reaction the structure **12** was given. The HRMS showed that it had a tetrameric structure ($C_{48}H_{56}O_8$, m/z 760.3936). Its ^{1}H NMR spectrum showed that it was not totally pure, probably contaminated by other stereoisomers. In this spectrum could be observed that **12** was a linear tetramer, which is formed by bonds between the C-4 of a chromane ring and C-6 of an aromatic ring of two different monomeric units, while a chromene ring remained unchanged as the end of the tetramer chain. The two hydrogens of this chromene ring, H-3‴ and H-4‴, appear as two doublets at δ_H 5.35 and 6.05 (J=10.0 Hz), and the corresponding carbons at δ_C 127.3 and 122.1, respectively. Thus, this tetramer **12** may be formed from the trimer **11** by reaction once more with another molecule of **1** as explained above for the formation of **11** from **10**.

We also obtained in low yield a mixture of linear pentamers, which was detected in the MS by a molecular ion at m/z 950 (100%) and fragments at m/z 760, 570, 380 and 191, which are formed by loss of a different number of precocene units. This mixture was also characterized in the ^{1}H NMR spectrum by signals of the ABX systems of the four chromane cycles and those due to the 3,4-double bond protons of the chromene ring.



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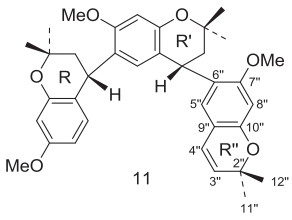

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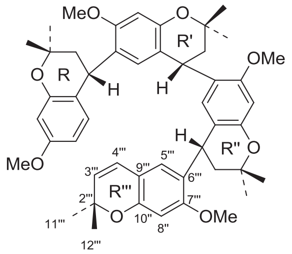

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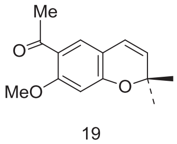

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