ON THE FACILE DIMERIZATION OF PRECOCENE II

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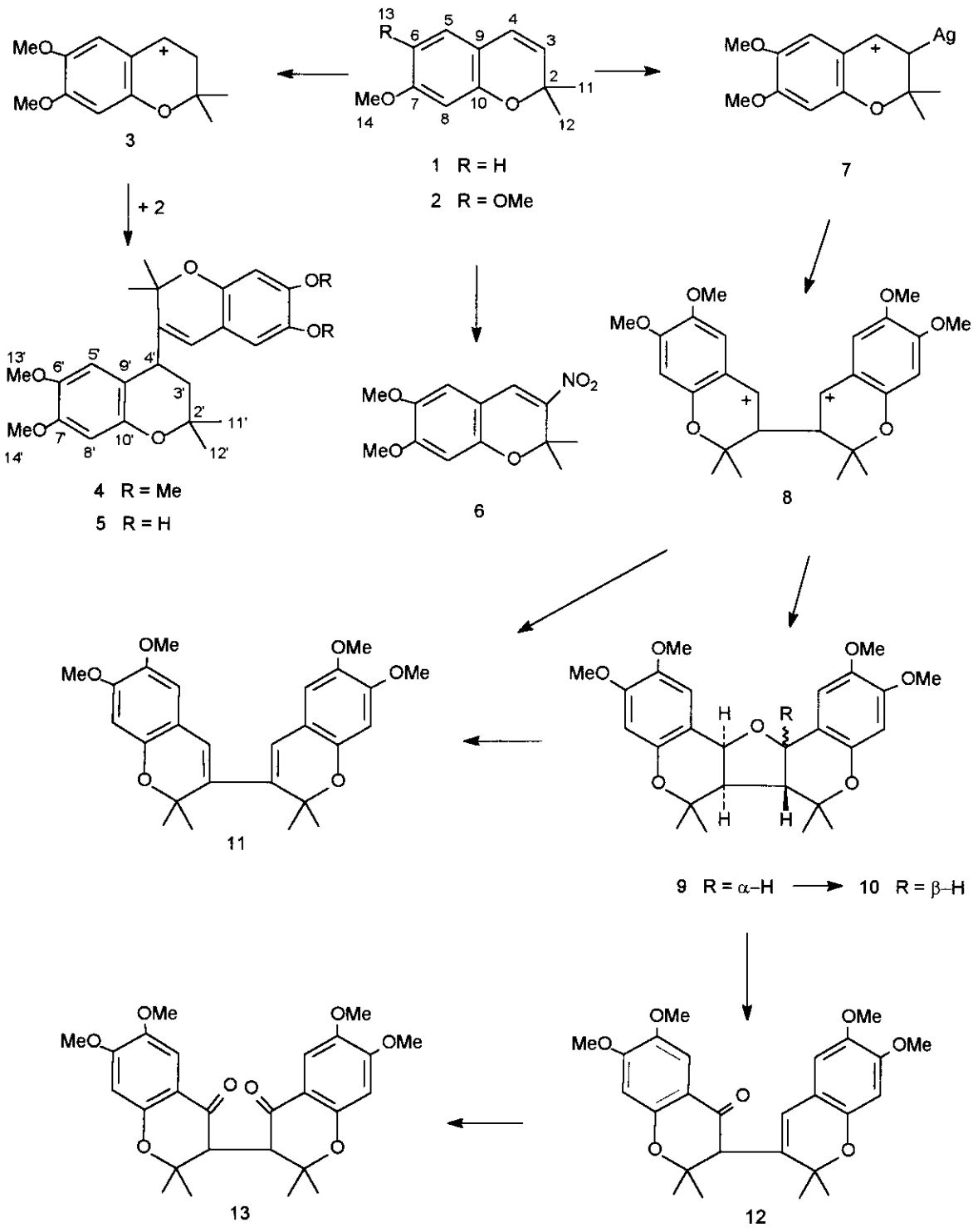
Abstract - The $AgNO_3$-silica gel dimerization of precocene II (**2**) has been restudied in order to identify minor products. The transformation of dimer B (**9**) into other dimeric compounds has also been examined.

Precocenes I (**1**) and II (**2**) are 2,2-dimethylchromenes, which have been isolated from *Ageratum houstonianum* (Compositae) and other species of this genus.[1-3] These substances possess antijuvenile hormone properties that produce precocious metamorphosis in insects.[3] They have also been shown to be hepatotoxic and nephrotoxic for mammals.[4,5] This bioactivity has been attributed to the formation, by cytochrome P450-dependent monooxygenases, of a highly reactive 3,4-epoxide that reacts readily with nucleophilic species. As a consequence of the interest of these chromenes we have prepared several dimers by treatment of precocene II (**2**) with Lewis acids.[6-8] The formation of these products is due to the fact that the chromene double bond of precocene II is also highly reactive.

In one of these works, when precocene II (**2**) was treated with $AgNO_3$-silica gel in petrol under different conditions, the dimers A (**4**), B (**9**) and C (**10**), the nitrochromene(**6**)and two unidentified minor dimers were obtained.[6] The formation of these compounds is shown in Scheme 1. While **4** was formed by acid dimerization[9] of **2**, dimers (**9**) and (**10**) occurred by oxidative one-electron coupling reaction.[6,8]

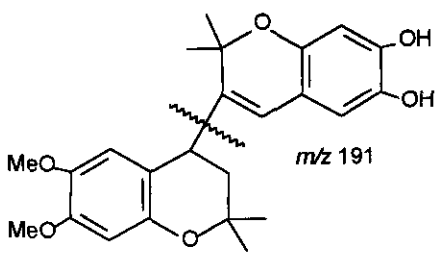
For the purpose of identifying the minor dimers we have repeated this reaction, increasing the reaction time. Thus, treatment of precocene II (**2**) in petrol with $AgNO_3$-silica gel gave dimer A (**4**), dimer B (**9**), dimer C (**10**) and the nitrochromene (**6**), as the main products, together with the demethylated dimer (**5**) and dimer G (**12**), as the minor ones.



Scheme 1

The structure of dimer (**5**) was assigned in the following way: The high resolution MS spectrum showed the molecular ion at m/z 412.1909 in accordance with the molecular formula $C_{24}H_{28}O_6$, thus indicating that it was a dimer. In its ^{1}H-NMR spectrum there appeared five singlets, due to four aromatic protons (δ 6.00, 6.02, 6.31 and 6.40) and one trisubstituted double bond (δ 6.22). Other signals observed in this spectrum corresponded to four methyls, two methoxy groups, a methine at δ 3.69 (dd, J = 12 and 6 Hz) and a methylene group with signals at δ 1.80 (t, J = 12 Hz) and 2.09 (dd, J = 12 and 6 Hz). Double resonance experiments showed that the hydrogens of these last two groups were coupled. All these data permitted us to assign to this product the structure (**5**), similar to that of dimer A (**4**), but with only two methoxy groups. These were located on the same aromatic ring, considering the cleavage observed in the mass spectrum with fragments at *m/z* 221.1212 ($C_{13}H_{17}O_3$) and 191.0709 ($C_{11}H_{11}O_3$) (Scheme 2). This was confirmed by the unambiguous assignment of its ^{1}H- and ^{13}C-NMR spectra, which was carried out by a two dimensional NMR study (COSY, HMQC and HMBC). With these data of **5** and those of dimers A (**4**) and C (**10**) the assignment of the ^{13}C-NMR spectra of precocene II derivatives[10] has now been completed.

On the other hand, we observed that when chloroformic solutions of dimer B (**9**) were left on the work bench or in a NMR tube this dimer was transformed into dimer C (**10**). With the purpose of studying this process we have irradiated chloroformic solutions of **9** with visible light. In this way, in addition to the dimer C (**10**), which was the main product, the 3,3'-dimer (**11**) (now named dimer J), dimer G (**12**) and dimer E (**13**) were also obtained. Compounds (**12**) and (**13**) had been isolated from the treatment of precocene II (**2**) with CrO_3 in water,[7] whilst the symmetrical dimer J (**11**) had been formed in the reaction of **2** with dry $FeCl_3$ in HOAc.[8]



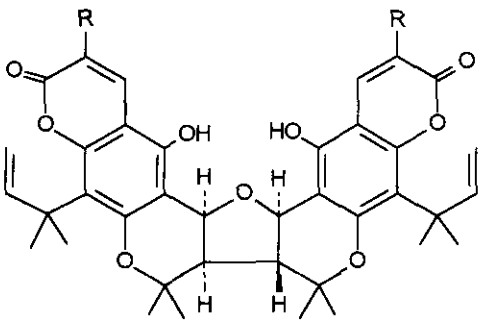
m/z 191

m/z 221 5

Scheme 2

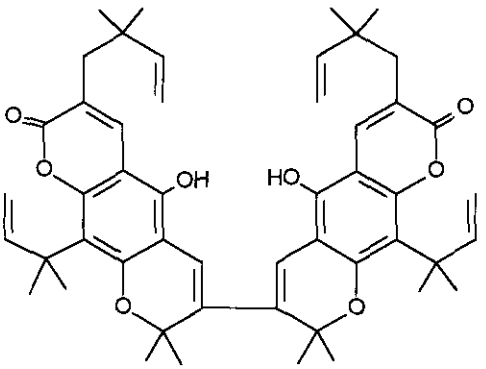
While precocene II dimers, such as **9-13**, have not been obtained from natural sources, the isolation of chromene-coumarin dimers has been reported. Thus, Furukawa *et al.*[11-14] have described the structures of dimeric chromene-coumarins, such as, furobinordentatin (**14**), furobiclausarin (**15**), bisclausarin (**16**) and

bishassanidin (**17**) isolated from *Citrus hassaku*. Analogies can be observed between the tetrahydrofuran connection in bicoumarins (**14**) and (**15**), and that of dimer B (**9**), between the chromene rings of bisclausarin (**16**) and dimer J (**11**), and likewise between the chromone rings of bishassanidin (**17**) and dimer E (**13**). Thus, we think that the dimerization reaction described here should be useful for the preparation of these bicoumarins and for the dimerization of other chromenes, that have an activated double bond.



14 R = H

15 R = 1,1-dimethylallyl



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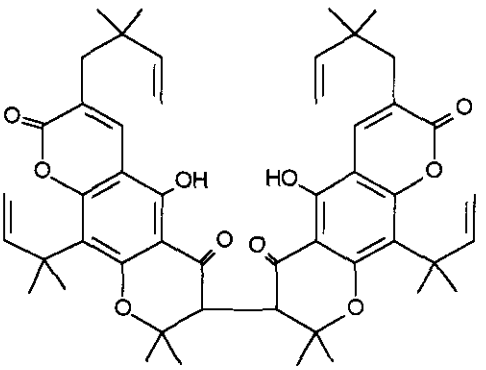

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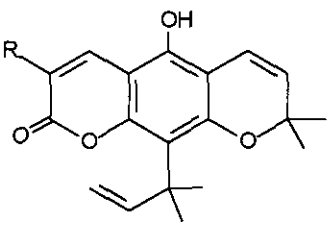

18 R = H

19 R = 1,1-dimethylallyl

EXPERIMENTAL

General experimental procedures

^{1}H-NMR spectra were recorded in $CDCl_3$ solutions at 500.13 MHz with a Bruker AMX2-500 spectrometer, and the ^{13}C-NMR spectra were run at 50.32 MHz with a Bruker AC-200. MS spectra were taken at 70 eV (probe) in a Shimadzu Q2000, and HRMS spectra in a Micromass Autospec spectrometer. Dry column chromatographies were made on Si gel Merck 0.02-0.063 mm.

Treatment of precocene II (2) with $AgNO_3$-silica gel

A mixture of II (**2**) (130 mg) in petrol (30 mL) and $AgNO_3$-silica gel (2:8) (140 mg) was stirred at rt in the dark for 48 h. The products were recovered by filtration. Evaporation of the solvent and chromatography of the residue on silica gel, eluting with petrol-EtOAc (8:2), afforded dimer A (**4**) (9 mg), dimer C (**10**) (38 mg), nitrochromene (**6**) (12 mg), dimer B (**9**) (18 mg), dimer G (**12**) (traces) and demethylated dimer A (**5**) (5 mg).

Dimer A (4): mp and MS, see ref.[6]; ^{1}H-NMR (500 MHz): δ 1.25 and 1.41 (each 3H, s, H-11' and H-12'), 1.50 and 1.56 (each 3H, s, H-11 and H-12), 1.80 (1H, t, J = 11 Hz, H-3'), 2.02 (1H, dd, J = 11 and 6 Hz, H-3'), 3.53 (1H, dd, J = 11 and 6 Hz, H-4'), 3.70 (3H, s, H-13'), 3.75 (3H, s, H-13), 3.81 (6H, s, H-14 and H-14'), 5.97 (1H, s, H-4), 6.37 (1H, s, H-8'), 6.40 (1H, s, H-5), 6.42 (1H, s, H-8) and 6.59 (1H, s, H-5'); ^{13}C-NMR (125 MHz): δ 23.7 and 29.8 (C-11 and C-12), 26.1 and 26.6 (C-11' and C-12'), 35.3 (C-4'), 43.4 (C-3'), 55.7 and 55.9 (C-14 and C-14'), 56.4 (C-13), 56.5 (C-13'), 74.3 (C-2'), 79.2 (C-2), 100.7 (C-8), 101.1 (C-8'), 109.2 (C-5), 112.4 (C-5'), 114.2 (C-9 and C-9'), 1211.1 (C-4), 128.1 (C-3), 142.7 (C-6'), 143.2 (C-6), 145.9 (C-10), 148.5 (C-10'), 148.8 (C-7'), 149.2 (C-7).

Demethylated dimer A (5): $[M]^+$ at *m/z* 412.1909, $C_{24}H_{28}O_6$ requires 412.1886; ^{1}H-NMR (500 MHz): δ 1.29 and 1.45 (each 3H, s, H-11'and H-12'), 1.67 and 1.79 (each 3H, s, H-11 and H-12), 1.80 (1H, t, J = 12 Hz, H-3'), 2.09 (1H, dd, J = 12 and 6 Hz, H-3'), 3.69 (1H, dd, J = 12 and 6 Hz, H-4'), 3.72 (3H, s, H-13'), 3.84 (3H, s, H-14'), 6.00 (1H, s, H-8), 6.02 (1H, s, H-5), 6.22 (1H, s, H-4), 6.31 (1H, s, H-5') and 6.40 (1H, s, H-8'); ^{13}C-NMR (125 MHz): δ 23.5 and 29.3 (C-11 and C-12), 27.3 and 28.8 (C-11' and C-12'), 36.6 (C-4'), 43.5 (C-3'), 55.8 (C-14'), 56.7 (C-13'), 74.2 (C-2'), 83.0 (C-2), 101.6 (C-8'), 108.0 (C-8), 111.7 (C-5'), 111.8 (C-9), 120.4 (C-4), 122.1 (C-5), 128.7 (C-3), 143.2 (C-6 and C-6'), 148.7 (C-10'), 149.8 (C-7'); EIMS *m/z* (rel. int.): 412 $[M]^+$ (48), 397 (100), 381 (33), 367 (9), 341 (6), 322 (28), 221 (38), 205 (17), 191 (9), 171 (19), 149 (20).

Dimer C (10): *mp and MS, see ref.*[6]; ^{1}H-NMR (500 MHz): δ 1.35 and 1.43 (each 6H, s, H-11, H-11' and H-12, H-12'), 2.42 (2H, d, J = 6.3 Hz, H-3 and H-3'), 3.84 and 3.85 (each 3H, s, H-13, H-13' and H-14, H-14'), 4.74 (2H, d, J = 6.3 Hz, H-4 and H-4'), 6.40 (2H, s, H-8 and H-8'), 6.83 (2H, s, H-5 and H-5'); ^{13}C-NMR (125 MHz): δ 24.0 and 27.8 (C-11, C-11' and C-12, C-12'), 49.1 (C-3 and C-3'), 55.8 (C-13 and C-13'), 56.3 (C-14 and C-14'), 72.2 (C-4 and C-4'), 76.2 (C-2 and C-2'), 100.9 (C-8 and C-8'), 111.5 (C-5 and C-5'), 113.2 (C-9 and C-9'), 143.9 (C-6 and C-6'), 147.6 (C-10 and C-10'), 149.8 (C-7 and C-7').

Transformation of dimer B

Dimer B (**9**) (200 mg) in $CHCl_3$ (30 mL) under stirring, was irradiated with visible light, Philips MLU 300. The reaction was stopped after 4.5 h, when the starting material had disappeared. The solvent was evaporated and the residue chromatographed eluting with petrol-EtOAc (8:2). The elution order was

dimer J (**11**) (18 mg), dimer G (30 mg) (**12**), dimer C (**10**) (110 mg) and dimer E (**13**) (20 mg).

Dimer J (11): IR, UV, and MS, see ref.[8]; ^{13}C-NMR see ref.[10]; ^{1}H-NMR (500 MHz): δ 1.54 and 1.56 (each 6H, s, H-11,H-11' and H-12, H-12'), 3.85 and 3.87 (each 6H, s, H-13, H-13' and H-14, H-14'), 6.21 (2H, s, H-8 and H-8'), 6.48 (2H, s, H-5 and H-5'), 6.57 (2H, s, H-4 and H-4').

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