# THE THERMAL DIMERIZATION OF PYRANO[3,2-*c*]COUMARINS[1]

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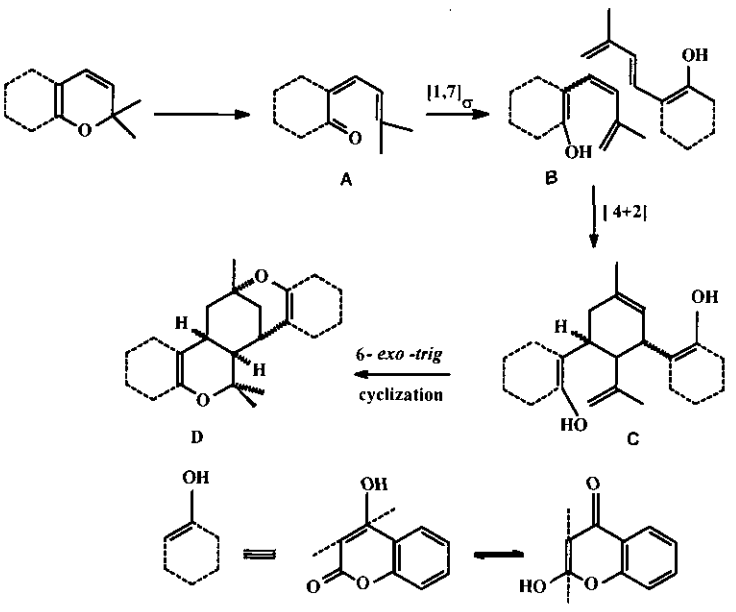
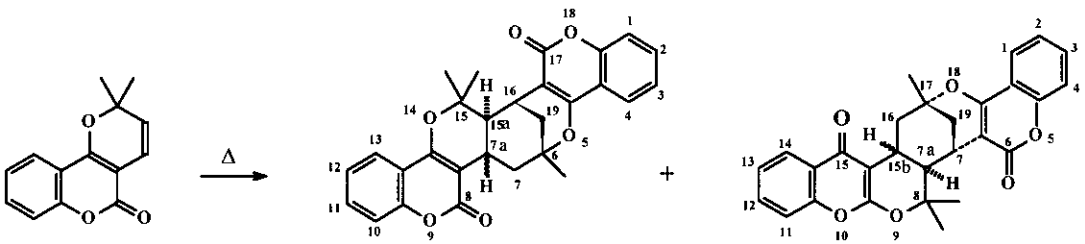
***Abstract*** -The thermal dimerization of the pyrano[3,2-*c*]coumarin (**1**) gave a mixture of four dimeric compounds, whose structure was established by extensive NMR studies.

The thermal dimerization of fused 2,2-dimethyl-1*H*-pyrans is a fascinating reaction, involved in the biogenesis of certain rutaceous alkaloids.[2] The reaction proceeds in several steps commencing with the electrocyclic ring opening of the pyran ring to a dienone (**A**). The latter is converted by a 1,7-sigmatropic shift into a trienol (**B**), which dimerises *via* a Diels-Alder cycloaddition. The enol hydroxyls then add to the olefinic double bonds, eventually affording the [2,6]methanopyrano[2,3-*d*]oxocin core of the adducts. The reaction affords mixtures of products, resulting from the presence of diastereomeric forms of the trienol moiety acting as the 2π-component. However, the 4π-component always reacts as the *E*-diastereomer, and the regiochemical control is excellent, since only the adducts with a *meta* relationship between the rings bearing the enol hydroxyls are formed (cf **C** in Scheme ).[3]



The crucial step is the 1,7-sigmatropic shift that turns the dienone system into a trienol. This reverts the electronic distribution of the system and generates the activated 4π-component for the cycloaddition reaction. Stabilization of the enol form is required, and this can be achieved by aromaticity (*e.g.* chromenes,[4] pyrano[3,2-*c*]acridines,[5] naphtho[2,1-*b*]pyrans[6]) or conjugation with a carbonyl group (pyrano[3,2-*c*]quinolinones[3]). In this case, the presence of tautomeric forms is a further source of complication, since the final trapping can occur in topologically different ways, involving the enol form of a ketone or of an amide carbonyl.[3,4]

We have now investigated the thermal dimerization of the pyrano[3,2-*c*]coumarin (**1**) , the lower prenylogue of the haemorrhagic coumarin ferprenin.[7] **1** is available in one step from condensation of 4-hydroxycoumarin with 3-methyl-2-butenal,[8] and represents a model compound for a class of coumarins found in plants of the *Umbelliferae* family. The study of the thermal dimerization of **1** was prompted by the discovery of the outstanding anti-HIV properties of certain pyranocoumarins[9] and of the Diels-Alder adducts of 2,2-dimethyldihydropyrans.[10] Furthermore, no data on the thermal dimerisation of pyrano[3,2-*c*]coumarins were available, in spite of the wealth of published information on their nitrogen isosters (pyranoquinolinones).[3] It was thus interesting to compare the reactivity of compounds of the two classes.



**1** → Δ → **2** β H, **3** α H + **4** β H, **5** α H

The thermolysis of **1** ( 150 °C, 48 h) under vacuum gave a mixture of four compounds ( **2-5**) , which could be separated by HPLC. The isolated compounds had the same molecular formula ($C_{28}H_{24}O_6$, MS), corresponding to the dimerization of the starting material. To assess the structure of these dimers, extensive NMR measurements were carried out. At 400 MHz all protons could be clearly resolved into first-order or *pseudo* first-order spin patterns, and the spectra could be completely analysed. The C-H correlations in the 2D NMR experiments located the proton-bearing carbons and the COLOC experiments (two-to four bond heteronuclear couplings) located the quaternary carbons.

Comparison of the spectra of **2-5** revealed that these compounds share the same spin systems and only differ for the stereochemistry of the ring junctions and/or the coumarin/chromone nature of the terminal heterocyclic systems. The spectroscopical considerations crucial to the structural elucidation can be summarized as follows:

1. *Distinction between coumarin and chromone moieties.* The "coumarin" δ-lactone carbon resonates around 160-165 ppm, while the "chromone" enone carbonyl resonates at lower fields (δ 175-180 ppm). Inspection of the $^{13}C$ NMR spectra showed that the dimers (**2**) and (**3**) are homogeneous and bear coumarin moieties, whereas **4** and **5** are the combination of a coumarin and a chromone units, whose location relative to the central bridgehead core was assessed by the inspection of long-range $^{1}H$ -$^{13}C$ correlations (COLOC spectrum).

2. *Stereochemistry of the fused rings junction.* This was assessed by inspection of the coupling constant between the ring junction methines. Thus, (**2**) ($J_{7a,15a}$) and (**4**) ($J_{7a,15b}$) showed a high value (>12 Hz) for these coupling constant ($J_{7a,15a}$), diagnostical for a *trans*-diaxial interaction. Conversely,(**3**) and (**5**) showed a smaller value (6.5 Hz), consistent with a synclinal *cis*-relationship.

3. *Stereochemistry of the bridgehead ring junction.* The oxocine ring system requires a *cis*-relationship between the bridgehead substituents, but two cases are possible, depending on the orientation of the bridgehead carbon relative to the protons at the fused ring junction. This issue was solved by inspection of the NOE effects (ROE spectrum). Thus, (**2**) and (**4**) showed a NOE interaction between the *pro-R* bridge methine and the ring junction proton on the γ-carbon (H-7a in (**2**), H-15b in (**4**)) whereas in (**3**) and (**5**) this interaction was not present.

Compared to the thermal dimerization of isosteric pyranoquinolinones,[3] (**1**) afforded a very similar reaction mixture, since chromone-chromone dimers were not formed, and the reaction showed a certain stereoselectivity as regards the configuration at the ring junctions. The full assignment of all the $^{1}H$- and $^{13}C$ NMR signals of (**2-5**) will help the structural elucidation of natural and synthetic dimeric pyrans of the oxocin type.

## EXPERIMENTAL PART

$^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker AMX 400 , $^{1}H$ frequency 400.13 MHz , $^{13}C$ frequency 100.61 MHz , $CDCl_3$ as solvent. Electrospray Ionization mass spectra ( ESI -MS ) were obtained on a Finnigan TSQ700 ( positive mode: $H_2O$ - MeOH as solvents).

Thermolysis of **1.** Compound ( **1**) (400 mg, 0,11 mmol) was heated at 150 $^0$C under vacuum ( 1.33 Pa , Kugelrohr apparatus) following the disappearance of the starting material by TLC (hexane - EtOAc 3:2). After 48 h the reaction mixture was dissolved in hexane - ether 1:1 ( 50 mL ) and filtered to remove the polymeric material . After evaporation of the solvents, the residue was separated by silica gel column chromatography. (hexane - EtOAc , 9:1 - 1:1 ) to give a mixture of the dimers (**2 - 5**) ( 275 mg ). which was separated by HPLC (Microporasil$^R$ , hexane - EtOAc 7:3 as eluant ) to give **2** ( 61 mg ), **3** ( 64 mg ), **4** ( 70 mg ) and **5** ( 30 mg ).

Dimer (**2**). Colourless, amorphus solid. ESI-MS : 457 ( M+H )$^+$ (100 %) ; 479 ( M + Na )$^+$; 511 ( M + Na + MeOH)$^+$ . $^1$H NMR $\delta_H$ 7.27 ( dd, J= 7.2 , 1.3 Hz, H-1), 7.49 ( ddd, J= 8.3 , 7.2 , 1.6 Hz, H-2), 7.25 ( ddd, J= 8.3 , 8.1 , 1.3 Hz, H-3), 7.79 ( dd, J= 8.1 , 1.6 Hz, H-4), 3.75 (dd , J= 15.0 , 4.2 Hz, H-7β), 1.49 (dd, J= 15.0 , 13.4 Hz, H-7α), 2.56 ( ddd, J= 13.4 , 12.0 , 4.2 Hz, H-7a), 7.24 (dd, J= 8.3 , 1.0 Hz, H- 10), 7.47 ( ddd, J= 8.3 , 7.3 , 1.5 Hz, H-11), 7.49 ( ddd, J= 8.3 , 7.2 , 1.6 Hz, H- 12 ), 7.75 ( dd, J= 8.0 , 1.5 Hz, H-13 ), 1.63 ( dd, J= 12.0 , 3.0 Hz, H-15a), 3.11 ( ddd, J = 3.4 , 3.0 , 2.7 Hz, H-16), 2.12 ( dd, J= 13.9 , 3.4 Hz, H-19a ), 1.56 (dd, J= 13.9 , 2.7 Hz H-19b ), 1.75 (s, 6 - Me ), 1.37 ( s, 15 - Me), 1.89 ( s, 15 - Me ). $^{13}$C NMR $\delta_C$ 116.2 ( d, C-1 ), 131.4 ( d, C-2 ), 123.4 ( d, C-3 ), 122.4 ( d, C-4 ), 115.8 ( s, C-4a), 158.1 ( s, C-4b ), 79.2 ( s, C-6 ), 39.0 ( t, C-7 ), 24.9 ( d, C-7a ), 101.2 ( s, C-7b), 161.4 (s, C-8 ), 152.4 ( s, C-9a), 116.0 ( d, C-10 ), 131.4 ( d, C-11 ), 123.5 ( d, C-12 ), 122.7 ( d, C- 13 ), 115.5 (s, C-13a), 159.5 ( s, C-13b), 82.9 ( s, C-15 0, 52.0 ( d, C-15a), 25.1 ( d, C-16 ), 107.6 ( s, C-16a ), 161.3 ( s, C-17 ), 152.4 ( s, C-18a ), 30.3 ( t, C-19 ), 28.9 ( q, 6-Me ), 28.1 ( q, 15-Me ), 20.8 ( q, 15-Me )..Anal. Calcd for $C_{28}H_{24}O_6$ : C, 73.66 ; H, 5.30 . Found : C, 73.75 ; H, 5.44 .

Dimer (**3**) : Colourless , amorphus solid . ESI - MS : 457 ( M+H)$^+$ ( 100% ) ; 479 ( M+Na )$^+$; 511 ( M+Na+MeOH)$^+$ . $^1$H NMR $\delta_H$ 7.30 ( dt, J= 8.3 , 1.2 Hz, H-1 ), 7.52 ( ddd, J= 8.3 , 7.2 , 1.8 Hz, H-2 ), 7.31 ( ddd, J= 8.3 , 7.2 , 1.2 Hz, H-3 ), 7.90 ( dd, J= 8.3 , 1.8 Hz, H-4 ), 3.23 ( ddd, J= 14.5 , 6.2 , 2.8 Hz, H-7β), 1.61 ( dd, J= 14.5 , 12.9 H-7α ), 3.16 (ddd, J=12.9, 6.5, 6.2 Hz, H-7a), 7.35 ( dd, J = 7.1 , 1.0 Hz, H-10 ), 7.58 ( ddd, J= 8.4 , 7.1 , 1.7 Hz, H-11 ), 7.34 ( ddd, J= 8.4 , 8.4 , 1.0 Hz, H- 12), 8.09 ( dd, J= 8.4, 1.8 Hz, H-13 ), 2.24 ( d, J= 6.5 Hz, H-15a), 3.48 ( m, H-16 ), 2.18 ( dd, J= 14.0 , 2.8 Hz, H-19a), 1.82 ( dt, J= 14.0 , 2.8, 2.8 Hz, H-19b), 1.58 (s, 6-Me ), 1.83 ( s, 15- Me).$^{13}$ C NMR $\delta_C$ 116.3 ( d, C-1 ), 131.5 ( d, C-2 ), 123.6 ( d, C-3 ), 122.9 ( d, C-4),115.7 ( s, C-4a ), 161.4 ( s, C-4b ), 78.2 ( s, C-6 ), 39.3 ( t, C-7), 24.9 ( d, C-7a ), 162.3 ( s, C-8), 152.8 ( s, C-9a), 116.8 ( d, C-10 ) , 132.6 ( d, C-11 ), 124.7 ( d, C-12 ), 125.3 ( d, C-13 ), 122.4 ( s, C-13a), 177.4 (s, C-13b), 84.8( s, C-15), 43.4 ( s, C-15a ), 27.2 ( d, C-16), 103.6 (s, C-16a), 161.7 (s, C-17 ), 152.5 (s, C-18a ), 31.8 ( t, C-19 ), 24.7 ( q, 6-Me ), 28.6 ( q, 15-Me ), 28.1 ( q, 15-Me ). Anal. Calcd for $C_{28}H_{24}O_6$ : C, 73.66 ; H 5.30 . Found : C, 73.28 ; H, 5.12 .

Dimer (4) .Colourless , amorphus solid. ESI - MS : 457 ( M+H )$^+$ ( 100 % ); 479 ( M+ Na )$^+$; 511 ( M+ Na + MeOH )$^+$; 935 (2M+ Na)$^+$ .$^1$H NMR $\delta_H$ 7.79 ( dd, J= 8.0 , 1.6 Hz, H-1 ), 7.25 ( ddd, J= 8.0 , 7.3 , 1.1Hz, H-2 ), 7.50 ( ddd, J= 8.4 , 7.3 , 1.6 Hz, H-3 ), 7.28 ( dd, J= 8.4 , 1.1 Hz, H-4 ), 3.06 ( ddd, J= 3.4 , 2.6 , 3.1 Hz, H-7), 1.66 ( dd, J= 12.3 , 3.1 Hz, H-7a ), 7.32 ( dd, J= 8.8 ,1.0 Hz, H-11 ), 7.57 ( ddd, J= 8.8 , 7.3 , 1.7 Hz, H-12 ), 7.34 ( ddd, J= 7.9 , 7.3 , 1.0 Hz, H-13 ), 8.09 ( dd, J= 7.9 , 1.7 Hz, H- 14 ) , 2.68 ( ddd, J= 13.1 , 12.3 , 4.2 Hz, H-15b ), 1.48 ( dd, J= 15.1 , 13.1 Hz, H-16α), 3.99 ( dd, J = 15.1 , 4.2 Hz, H-16β), 2.15 ( dd, J= 13.8 , 3.4 Hz, H-19a ), 1.55 ( dd, J= 13.8 , 2.6 Hz, H-19b ), 1.88 ( s, 8-Me ), 1.42 ( s, 8-Me ), 1.77 (s, 17-Me ). $^{13}$ C NMR $\delta_C$ 122.4 ( s, C-1 ), 123.5 ( d, C-2 ) , 131.4 ( d, C-3 ), 116.2 ( d, C-4 ), 152, 4 ( s, C-4a ), 161.4 ( s, C-6 ), 107.6 ( s, C-6a ), 25.0 ( d, C-7 ), 52.5 ( d, C-7a ) , 86.0 ( s, C-8 ),163.0 (s, C-9a ), 152.6 ( s, C-10a ) , 116.6 ( d, C-11 ), 132.5 ( d, C-12), 124.6 (d, C-13), 125.3 ( d, C-14 ), 122.8 ( s, C-14a ), 177.5 ( C-15), 97.0 ( s, C-15a ) , 24.9 ( d, C-15b ), 39.0 ( t, C-16 ), 79.4 ( s, C-17 ), 158.2 ( s, C-18a ), 115.8 ( s, C-18b ), 30.3 ( t, C-19 ), 28.0 ( q, 17-Me ) , 20.6 ( q, 8-Me ), 28.8 ( q, 8-Me ). Anal. Calcd for $C_{28}H_{24}O_6$ : C, 73.66; H, 5.30 . Found : C, 74.01 ; H, 5.28 .

Dimer (5) . Colourless, amorphus solid. EIS -MS :457 ( M+H)$^+$, 479 ( M+Na)$^+$ ( 100 %), 495 ( M+K)$^+$, 935 ( 2M+Na)$^+$, 1392 (3M+Na)$^+$. $^1$H NMR $\delta_H$7.88 ( dd, J= 8.8 , 1.6 Hz, H-1 ), 7.31 ( ddd, J= 8.0 , 7.3 , 1.1 Hz , H-2 ), 7.52 ( ddd, J= 8.4 , 7.3 , 1.6 Hz, H-3 ), 7.30 ( dd, J= 8.4 , 1.1 Hz, H-4 ), 3.52 (m, H-7 ), 2.24 ( dd, J= 6.5 , 3.5 Hz, H-7a ), 7.25 ( dd, J= 8.8 , 1.0 Hz, H-11 ) 7.48 ( ddd, J= 8.8 , 7.3 , 1.7 Hz, H-12), 7.26 ( ddd, J= 7.9 , 7.3 , 1.0 Hz, H-13 ), 7.79 ( dd, J= 7.9 , 1.7 Hz, H- 14 ), 2.95 ( ddd, J= 12.9 , 6.5 , 5.5 Hz, H-15b), 1.65 ( dd, J= 14.1 , 12.9 Hz, H -16α ), 3.11 ( ddd, J= 14.1 , 5.5 , 2.6 Hz, H-16β), 2.21 ( dd, J= 13.9 , 2.8 Hz, H- 19a), 1.81 (ddd, J= 13.9 , 2.8 , 2.6 Hz, H- 19b ), 1.84 ( s, 8- Me ), 1.57 ( s, 8- Me ), 1.58 ( s, 17 -Me ). $^{13}$ C NMR $\delta_C$ 122.8 ( d, C-1), 123.6 ( d, C-2), 131.5 ( d, C-3 ), 116.3 (d, C-4 ), 152.2 ( s, C-4a ), 161.6 ( s, C- 6 ), 103.6 ( s, C-6a ), 27.2 ( d, C-7 ), 43.2 ( d, C-7a ), 81.0 ( s, C-8 ), 162. 1 ( s, C-9a ), 152. 5 ( s, C-10a ), 116.1 ( d, C- 11 ), 131. 3 ( d ,C-12 ), 123.5 (d, C-13), 122.7 ( d, C-14 ), 115.1 ( s, C-14a ), 178 ( s, C-15 ) , 101.9 ( s, C-15a), 25.5 ( d, C- 15b), 38.8 ( t, C-16 ), 78.2 ( s, C-17 ), 161.3 ( s,C-18a ), 115.6 (s, C-18b ), 31.8 (t, C-19 ), 28.7 ( q, 8-Me ), 28.1 ( q, 8- Me ), 24.6 ( q, 17- Me ). Anal. Calcd for $C_{28}H_{24}O_6$ : C, 73.66 ; H, 5.30 . Found : C, 73.50 ; H, 5.32 .

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