ACID CATALYZED DIMERIZATION OF THE PYRANOCOUMARIN XANTHOXYLETIN: FORMATION OF A "DIELS-ALDER" DIMER ANALOGOUS TO THE PARAENSIDIMERINES

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Abstract--- Acid-catalyzed dimerization of xanthoxyletin has given, in low yield, a dimeric compound which has been identified as a Diels-Alder addition product in which the C-4' and C-3' positions of one monomer have linked, respectively, with one of the C-2' methyls and C-4' of the other. While a similar dimerization reaction is known in a number of pyranoquinolone alkaloids from the Rutaceae this is the first report of its occurrence among pyranocoumarins.

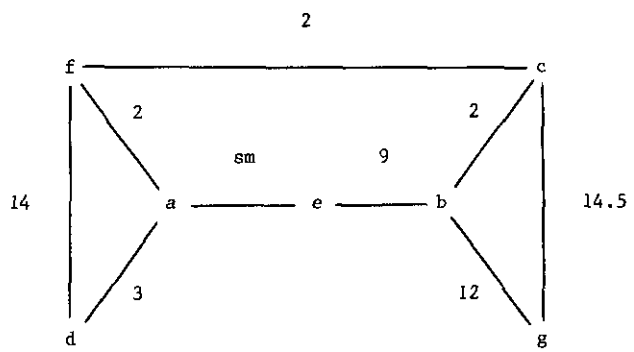
The plant family Rutaceae has yielded a number of dimeric alkaloids that appear to be derived by Diels-Alder addition reactions of prenylated precursors.[1] Typical examples are the paraensidimerines A (1, R = R_1= Hα), C (1, R = Hα, R_1= Hβ), E (1, R = Hβ, R_1= Hα) and F (1, R = R_1= Hβ) in which C-4' and C-3' of the dihydropyran ring I of the pyranoquinolone have become linked to one of the C-2' methyls and C-4' of the II pyran unit. Recently Ayafor et al.[2] have reported the synthesis of mixtures of the related vepridimerines by thermolysis of the corresponding monomer veprisine when sealed in a pyrex tube under reduced pressure and heated to 200-220°C for 15 h. Several dimeric prenylcoumarins have also been isolated as natural products from the Rutaceae[3] but all of these have structures based on 2 (R and R_1 = substituted coumarin nuclei). In this paper we report the results of a study of the outcome of heating the common pyranocoumarin xanthoxyletin (3) under acidic conditions. This was undertaken in order to ascertain whether dimerization could be induced by such conditions. It was anticipated that the most likely type of dimer to be formed would not be of the Diels-Alder type (cf. 1 and 2) but through oxidative coupling of the kind reported[4] to occur with the pyranoacridone acronycine (e.g. 4). The reaction employed was to reflux xanthoxyletin in varying concentrations of conc. HCl in MeOH for 24 h. In all experiments the bulk of the xanthoxyletin was recovered unchanged but in one case[5] a polar product (yield 3%) was isolated. The compound melted above 300°C and retained the spectral characteristics of a coumarin.[6] The EIMS indicated the molecular ion m/z 516 ($C_{30}H_{28}O_8$) and thus the occurrence of a xanthoxyletin dimer. The base peak at m/z 243 could be assigned to the pyranocoumarin monomer from which a CH_3 radical had been lost.

A high field ^{1}H nmr study[6] revealed two sets of signals for non-equivalent H-3, H-4, H-8 and

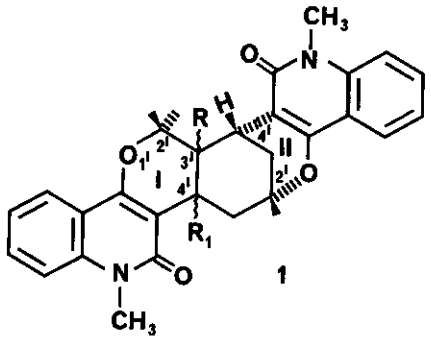
5-OMe substituents indicating that the coumarin nuclei of xanthoxyletin remained intact. Three C-Me resonances occurred as singlets at δ 1.69, 1.48 and 1.45 and the seven remaining protons as a series of discrete one-proton signals. These were subjected to decoupling experiments (Table 1) and their relationships were resolved to the pattern shown in Scheme 1 which is typical of the CH_2-CH-CH-CH-CH_2 system that arises in Diels-Alder-type addition reactions involving pyranoquinolone alkaloids.[1] A significant feature of this system is the long range W-bond coupling between H_c and H_f, the equatorial protons of the two methylenes. This requires that the cyclohexane ring generated by the addition has the chair conformation. From the relatively shielded resonance of the central (H_e) proton it was confirmed that the addition had involved C-4' to C-2' methyl and C-3' to C-4' (5) in which the other methine protons (H_a and H_b) are deshielded by the adjacent aromaticnuclei. The alternative product of C-4' to C-4' and C-3' to C-2' methyl addition (6) would leave H_a and H_b in shielded positions with H_e deshielded.

Table 1. ^{1}H nmr: Details of chemical shifts and coupling patterns for the seven methine/methylene protons. For remainder of spectrum see reference 6.

Proton		Multiplicity	J value(s)	Interactions
a	3.61	broad s	-	d, e, f (all sm)
b	3.01	ddd	12, 9, 2	c(2), e(9), g(12)
c	2.81	ddd	14.5, 2, 2	b(2), f(2), g(14.5)
d	2.13	dd	14, 3	a(3), f(14)
e	2.11	broad d	9	b
f	1.75	ddd	14, 2, 2	a(2), c(2), d(14)
g	1.69	dd	14.5, 12	b(12), c(14.5)



Scheme 1. Proton connectivities with J values (sm = small J).



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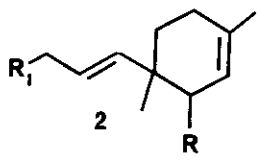

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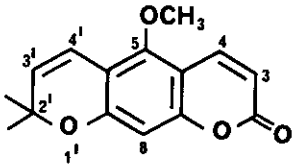

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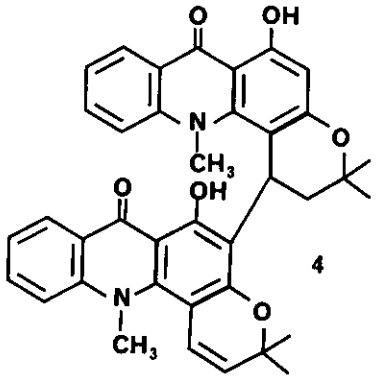

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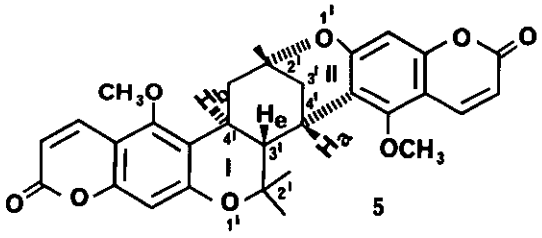

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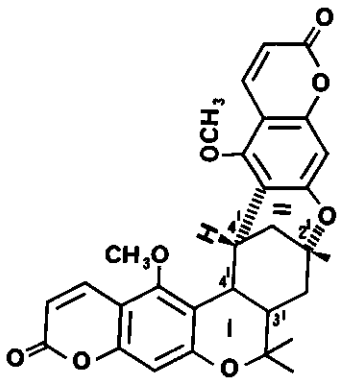

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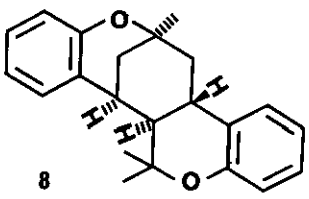

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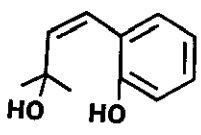

7

Coupling constants between methylene and adjacent methine protons require that H_b be axial while H_a is equatorial. On this basis H_f and H_d must be assigned to the II-3' methylene and H_a to II-4' as the II-4'/II-2'-methyl addition must involve participation of the axial II-4' bond and the axial 2'-methyl.[1] Consequently II-H-4' must be equatorial.

These arguments, together with the observation that W-bond coupling between H_c and H_f places the cyclohexane ring in the chair conformation, reduce the possible structures to two in which the addition to the I-pyran ring results in a cis or a trans relationship between I-H-4' and I-H-3'. The coupling constant of 9 Hz between H_b and H_e clearly indicates the trans configuration and allows the assignment of structure 5 (stereochemistry relative, not absolute).

Chromatographic analysis failed to indicate the occurrence of other Diels-Alder dimers. A comparable acid treatment of 7 also gave a single trans-substituted dimer (8)[7], analogous to 5. By contrast the thermolytic conditions adopted by Ayafor et al.[2] gave a mixture of products with differing stereochemistries around the cyclohexane ring.

REFERENCES AND NOTES

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2. J. F. Ayafor, B. L. Sondengam, J. D. Connolly, and D. S. Rycroft, Tetrahedron Letters, 1985, 26, 4529.
3. A. I. Gray, in "Chemistry and Chemical Taxonomy of the Rutales", P. G. Waterman and M. F. Grundon, eds., Academic Press, London, 1983, pp. 97-146.
4. S. Funayama and G. A. Cordell, Heterocycles, 1983, 20, 2379.
5. Xanthoxyletin (500 mg) was refluxed with conc. HCl (40 ml) in MeOH (20 ml) for 24 h. The reaction mixture was cooled and extracted into $CHCl_3$. The $CHCl_3$-soluble material was subjected to column chromatography over silica gel eluting with 25% EtOAc in petrol (bp 40-60) to remove xanthoxyletin. The column was then washed with EtOAc to remove 5 (15 mg).
6. Xanthoxyletin dimer (5), recrystallised from MeOH as needles, mp > 306°. $[\alpha]_D$ 0.0°. UV λ max (MeOH) 248, 258, 335 (major band) nm. IR ν max (KBr disc) 1730, 1620, 1390, 1140, 1120, 820 cm^{-1}. EIMS (70eV, probe temp. 240) m/z (rel. int.) M^+ 516.1781; $C_{30}H_{28}O_8$ requires 516.1784 (57%), 501 (80%), 485 (22%), 461 (12%), 259/258 (36%), 243 (100%). ^1H nmr (360MHz, $CDCl_3$) δ 1.45, 1.48, 1.69 (3 x 3H, s, 3 x Me), 3.70, 3.93 (2 x 3H, s, 2 x OMe), 6.18, 6.20 (2 x 1H, 2 x d, J = 9.6 Hz, 2 x H-3), 6.53, 6.63 (2 x 1H, s, 2 x H-8), 7.77, 7.80 (2 x 1H, 2 x d, J = 9.6 Hz, 2 x H-4); for remainder of spectrum see Table 1.
7. C. S. Barnes, M. I. Strong, and J. L. Occolowitz, Tetrahedron, 1963, 19, 839.

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