

New Chromenes from *Eupatorium* Species

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It has been known for a long time that *Eupatorium* species contain benzofurans,¹ but the presence of chromenes has only been briefly mentioned.^{2,3} This communication now reports the isolation of six chromenes from extracts of Australian weeds from this genus, *E. riparium* Regel and *E. glandulosum* H.B. & K. (syn. *E. adenophorum* Spr.).

One of these, eupatoriochromene (1) (6-acetyl-7-hydroxy-2,2-dimethylchromene, m.p. 76°C), and the oily 7-methoxy-2,2-dimethylchromene have been reported by Sørensen and co-workers.²

The latter is co-existent with ageratochromene (6,7-dimethoxy-2,2-dimethylchromene) in the botanically closely related genus *Ageratum*⁴ (tribe Eupatorieae) while eupatoriochromene seems to be widely distributed in the genus *Eupatorium*. However, this compound was originally isolated from *Helianthella uniflora* Torr. & Grey.² It is therefore interesting to note that a recent paper⁵ reports the occurrence of methyleupatoriochromene (2) (encecalin) in another member of the tribe Heliantheae, *Encelia californica* Nutt.

In addition to eupatoriochromene (1) four related chromenes were isolated from *E. riparium* Regel. Their relationship was indicated by the NMR spectra (Table 1). Ripariochromene A (3) (m.p. 88.5°C) was shown by accurate mass measurements to have the molecular composition C₁₄H₁₆O₄ (Found: 248.1046. Calc. 248.1049). Its NMR spectrum clearly indicates the 2,2-dimethylchromene system (Table 1). The two methyl groups resonate as a six proton singlet at 8.50 τ and the two olefinic protons at C-3 and C-4 give rise to an AB-quartet ($J=10$ cps.) at 4.41 and 3.73 τ . In addition an acetylmethyl group (7.46), a strongly hydrogen-bonded hydroxyl proton (-2.80), a methoxy methyl group (6.11), indicative of an *ortho* hydroxyacetophenone structure and one aromatic proton (2.88) is clearly visible.

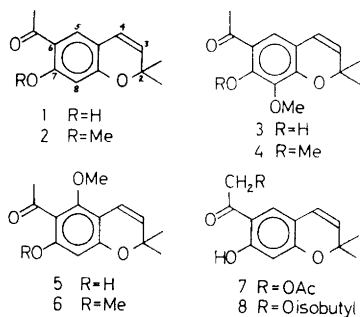
Ripariochromene A (3) thus shows a close relationship to evodionol⁵ (5) (m.p. 86°C), but direct comparison of spectra and chromatographic properties proved non-identity. The most obvious difference in the two NMR spectra (Table 1) is the τ value for the aromatic protons. Its low shift position in the spectrum of ripariochromene A (3) (2.88) indicates that the aromatic proton is in the *ortho* position to the acetyl group. Further evidence for this is to be found in the following. The acetyl methyl groups of evodionol (5) and 2-hydroxy-4,6-dimethoxyacetophenone which both are *ortho* hydroxyacetophenones with a methoxy group in the other *ortho* position, both show remarkably low shifts, 7.32 and 7.39, respectively. On methyla-

Table 1. The NMR spectra of the chromenes treated in this communication. Compounds 1-6 were dissolved in CDCl₃, 7 and 8 in CCl₄.

	2	3	4	5	6	7	8
Eupatoriochromene (1)	8.56	4.43	3.73	2.71	7.49	-2.68	3.69
Methyleupatoriochromene (2)	8.56	4.50	3.73	2.49	7.46	6.13	3.62
Ripariochromene A (3)	8.50	4.41	3.73	2.88	7.46	-2.80	6.11
Methylripariochromene A (4)	8.49	4.39	3.69	2.76	7.42	6.02	6.10
Evodionol (5)	8.54	4.41	3.51	6.18	7.32	-3.40	3.82
Methylevodionol (6)	8.57	4.48	3.51	6.22	7.52	6.24	3.80
Ripariochromene B (7)	8.57	4.45	3.77	2.82	^a	-1.97	3.68
Ripariochromene C (8)	8.59	4.49	3.81	2.84	^b	-1.93	3.71

^a 4.79 (s), 7.80 (s).

^b 4.77 (s), 7.52 (sept.), 8.78 (d).



tion of the hydroxy group these values are shifted by 0.20 and 0.17 ppm to 7.52 in methylevodionol (6) and 7.56 in 2,4,6-trimethoxyacetophenone. The average τ values of *ortho* hydroxyacetophenones with the other *ortho* position free is 7.46 and only negligible shifts occur on methylation. The reason for this effect is quite obvious. In the locked hydrogen bonded structure, the acetyl methyl group interacts with the neighbouring methoxy group. This interaction does not take place when the hydrogen bonding is released on methylation.

The corresponding τ values for ripariochromene A (3) and methylripariochromene A (4), 7.46 and 7.42, respectively, indicate that the acetyl group has only one *ortho* substituent.

An examination of the NMR spectra of a number of chromenes is summarized in Table 2.⁷ It shows the influence of the

Table 2. The influence of 5-substituents on the shift positions of the olefinic protons at C-3 and C-4 in a chromene.

Substituent at C-5	Mean τ value of proton at C-3	Mean τ value of proton at C-4
None	4.49	3.74
Hydroxyl, methoxyl	4.40	3.34
Carbonyl	4.27	2.84
O-Acetyl	4.34	3.65

nature of the 5-substituent on the τ values of the hydrogens at C-3 and C-4. According to this, ripariochromene A has no substituent at C-5 (4.41 and 3.73).

Now bearing in mind that ripariochromene A is an *ortho* hydroxyacetophenone and that the acetyl group has only one *ortho* substituent all possibilities other than the suggested structure 3 are excluded.

In benzene solution the acetyl and methoxy methyl groups showed Δ -values [$\Delta = \tau(\text{benzene}) - \tau(\text{CDCl}_3)$] of 0.54 and 0.01 ppm, respectively. This again indicates that the acetyl group has one *ortho* position unsubstituted and, moreover, that the methoxy group has both its *ortho* positions occupied. A detailed discussion of benzene shifts in this system has been published elsewhere.⁹

From *E. riparium* Regel there has also been isolated the oily methylripariochromene A (4) whose spectral properties are clearly indicative of its structure. (Found: 262.1204. Calc. for $C_{16}H_{18}O_4$: 262.1205). Its NMR spectrum (Table 1) shows that the hydroxy group in ripariochromene A is replaced by a methoxy group (6.02). The NMR spectra of 3 and 4 are otherwise very alike.

In addition to the above mentioned compound it has been isolated from the same plant an acetate, ripariochromene B (7) (m.p. 145–146°C, IR 1750 cm^{-1}) and an isobutyrate, ripariochromene C (8) (m.p. 109–110°C, IR 1740 cm^{-1}). Their NMR spectra suggest structural relationship to eupatoriochromene (1) (see Table 1). The NMR spectrum of the acetate reveals the presence of a methylene group (4.79) and an acetoxy methyl group (7.80). These singlets are in reasonable accordance with the corresponding signals in the NMR spectrum of *p*-phenyl-phenacylacetate (4.63, 7.76).

The NMR spectrum of the isobutyrate (8) shows the isopropyl group as a six proton doublet at 8.78 and a one proton septet at 7.52 ($J=7$ cps.). The molecular composition of the two chromenes as $C_{15}H_{16}O_5$ (Found: 276.1007. Calc. 276.0998) and $C_{17}H_{20}O_5$ (Found: 304.1309. Calc. 304.1310) is proved by accurate measurements of the molecular ion peaks. Both mass spectra show common features. Thus the major peaks are found at m/e 203 and m/e 201 due to $M - \text{CH}_2\text{R}$ and $M - 15 - \text{HR}$.

Significant peaks are also found at m/e 175 and m/e 160 ($M-\text{COCH}_2\text{R}$ and $M-15-\text{COCH}_2\text{R}$).

The molecular compositions of all peaks are proved by accurate mass measurements and the loss of HR is confirmed by metastable peaks at m^* 155 and m^* 140, respectively.

E. glandulosum H.B. & K. (syn. *E. adenophorum* Spr.) contained none of the above mentioned chromenes, but an oily component $\text{C}_{14}\text{H}_{16}\text{O}_3$ (Found: 232.1101. Calc. 232.1099). Its spectral properties were identical to methyleupatoriochromene A (2) formed on methylation of eupatoriochromene A (1) with dimethylsulphate and potassium carbonate.

NMR spectra were recorded on a Varian A-60-A spectrometer with CDCl_3 (Merck) as solvent. Mass spectral measurements were done on an AEI MS 902 instrument.

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Equilibrium Protonation of a Carbon Base Prior to its Hydrolysis. The Acid-catalyzed Cleavage of the Furan Ring

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In a previous study¹ of the hydronium ion-catalyzed hydrolysis of furan and 2,5-dimethylfuran, two alternative mechanisms were shown to be in accord with the experimental results. First, a rate-determining proton transfer with a Brønsted α of almost unity. Second, a protonation pre-equilibrium and subsequent heterolysis of the protonated substrate. Although the lack of detectable general acid catalysis and the measured solvent deuterium isotope effect, $k_{\text{D}_2\text{O}^+}/k_{\text{H}_3\text{O}^+}=2.15$, were best interpreted in the terms of the latter mechanism, the rate-determining proton transfer mechanism could not be wholly excluded.

Stamhuis *et al.*² have proposed that proton transfer is the rate-determining stage in the hydrolysis of furans. Unfortunately, this assumption is mainly based on the reported value of the solvent deuterium isotope effect, $k_{\text{D}_2\text{O}^+}/k_{\text{H}_3\text{O}^+}=0.59$, which greatly differs from the value determined by Salomaa and Kankaanperä.¹ (An explanation for this discrepancy is photochemical side reactions that take place when the reaction system is exposed to ultraviolet light.¹)

The above problem can be solved if it is possible to measure the rate of proton (or its isotopic equivalent) uptake by the substrate and the rate of ring cleavage, both under the same conditions. This paper presents such data. The kinetics of the deuterium uptake by 2-methylfuran (I) and the hydrolytic cleavage of the ring were studied in solutions of hydrochloric acid in a dioxane- D_2O mixture (3:1 w/w).

