The Mechanism of Intramolecular 'Citran' Bicyclisation of Chromens: Stereochemistry of a Forward (H^+ Catalysed) and a Related Reverse (Thermal) Process

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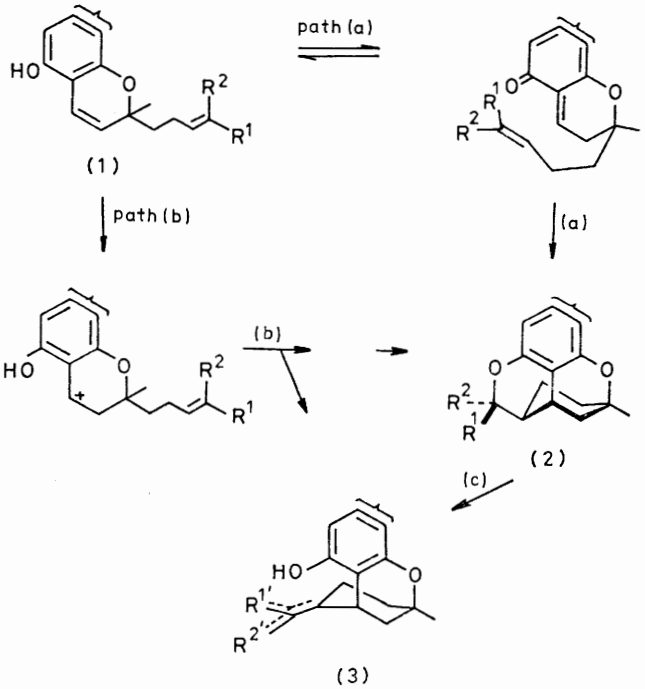
Summary Stereochemical evidence suggests that acid-catalysed citran formation proceeds *via* electrocyclisation of a dienone; pyrolysis of 'farnesylidenemalonic acid' proceeds with retention of configuration at the newly formed 8-olefin bond, indicating the operation of a retro-Diels–Alder process.

BICYCLISATION[1] of chromens of type (**1**) (from resorcinol–2,6-dienal condensations), yielding 'citrans' (**2**), is the only synthetic route to this natural ring-system and appears to be of biosynthetic importance. Reaction (**1**) → (**2**) may be induced by weak base (*e.g.* pyridine) or acid catalysis, but details of the latter process have been obscure and conflicting. When $R^1 \neq R^2$ in (**1**), three new chiral centres result and we have shown that in the pyridine-catalysed reaction the geometry of the acyclic double bond is retained in the product.[2] Path (a) of Scheme 1, an intramolecular [2 + 4] cycloaddition within a quinone-methide tautomer of the phenol, is consistent with this. However, in acid, the possibility of a non-stereospecific proton initiated process [path (b)] must be considered. This could lead to (**2**) together with its geometric isomer (R^1 and R^2 reversed), besides tricyclic products (**3**),[1] proceeding through carbocations of which only the first is shown. Because of the geometrical arrangement, a fully concerted acid-catalysed (**1**) → (**2**) conversion appears very unlikely.

We have now examined a system in which the stereochemistry of both acid- and base-catalysed cyclisations can be examined and compared. The first reaction studied was the pyridine-catalysed condensation between phloroglucinaldehyde (**4**) and 2*E*/*Z*,6*E*-farnesal (**5**) at 50 °C.†

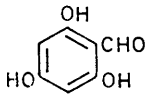


SCHEME 1.

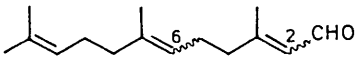
The products were the two regioisomeric citrans (**7a**) and (**7b**) (1 : 3), along with the chromen (**8a**). Using chemical shift criteria for the methyl at R^3 or R^4, developed in

† It has been established earlier that 2*E* or 2*Z*-configuration of the aliphatic aldehyde is immaterial in the chromenylation process.

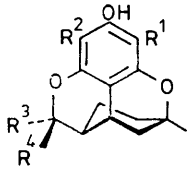
earlier work,[2] it was clear that both (**7a**) and (**7b**) retained the 6*E*-geometry of the original farnesal. Formation of *two* regioisomeric citrans has been rationalised as proceeding *via* electrocyclic opening of (**8a**), inversion of



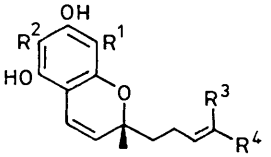
(4)



(5); 2*EZ*, 6*E* (6); 2*EZ*, 6*Z*



(7)



(8)

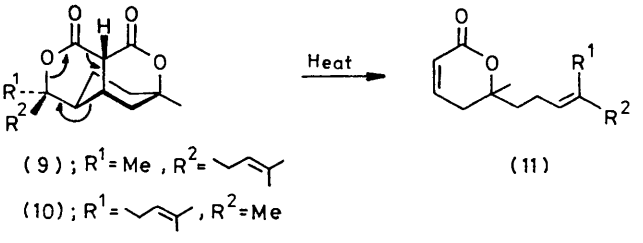
	R^1	R^2	R^3	R^4
a	CHO	H	Me	
b	H	CHO	Me	
c	CHO	H		Me
d	H	CHO		Me

dienone geometry, and reclosure in the alternative orientation (**8b**);[1,3] the latter, though not an observable product, serves as precursor to (**7b**). In a converse manner, (**4**) reacted with 2*E*/*Z*,6*Z*-farnesal (**6**) to give the chromen (**8c**) and the regioisomeric citrans (**7c**) and (**7d**), both retaining the 6*Z*-configuration. The four citrans (**7a**—**d**) were chromatographically and spectroscopically distinguishable.

The chromen (**8a**) was then refluxed in benzene with (+)-camphorsulphonic acid. Only two citrans were produced, (**7a**) and (**7b**) (1 : 1), the acyclic double bond geometry being retained though orientational rearrangement occurred. The difference in citran ratio between base and acid conditions is thought to reflect differences in thermodynamic stabilities between the ionised and protonated intermediates involved. Similar acid treatment of (**8c**) leads to the citran (**7c**) only, the 6-geometry (*Z*) again being retained. The chromen (**8c**) reacts with acid more rapidly than (**8a**) and since only one citran is found in this case, the more readily occurring bicyclisation apparently becomes faster than the rate-determining step of the reorientation process.

Thus despite complexities in the reactions, both the acid- and the base-catalysed bicyclisations are stereospecific and it becomes reasonable to view both types of reaction as proceeding through an *o*-quinone methide, followed by intramolecular [2 + 4] cycloaddition. The processes then differ only in the mode of catalysis of the *o*-hydroxystyrene–*o*-quinone methide tautomerism. The tricyclic products (**3**) may arise by the well established acid-induced cleavage of the citrans (**2**) [Scheme 1, path (c)].[1]

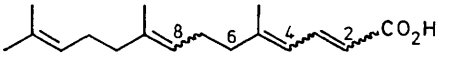
The reverse citran → chromen reaction has not been observed for aromatic citrans. However, pyrolysis of the bis-lactonic citran 'citrylidenemalonic acid' to 5,9-dimethyldeca-2,4,8-trienoic acid[4] appears to be initiated by such a retro-Diels–Alder process and should be stereospecific with respect to the formation of the 8-double bond. As a test of this we have employed the corresponding 'farnesylidenemalonic acids' (**9**) and (**10**) from 6*E*- and 6*Z*-farnesal respectively.[2,4] Pyrolysis of (**9**) (200 °C; Cu bronze; 3 h) afforded four isomers of 5,9,13-trimethyltetradeca-2,4,8,12-tetraenoic acid (**12**), all 8*E*. Conversely pyrolysis of (**10**) gave the four 8*Z*-stereoisomers (Scheme 2).‡



(9); R^1 = Me, R^2 =

(10); R^1 = , R^2 = Me

(11)



(12)

Heat
(9) ⟶ 2*Z*,4*E*,8*E* 16%
2*Z*,4*Z*,8*E* 14%
2*E*,4*Z*,8*E* 40%
2*E*,4*E*,8*E* 30%

Heat
(10) ⟶ 2*Z*,4*E*,8*Z* 14%
2*Z*,4*Z*,8*Z* 16%
2*E*,4*Z*,8*Z* 40%
2*E*,4*E*,8*Z* 30%

SCHEME 2.

Thus this type of pyrolysis may reasonably be viewed as a reverse cycloaddition to the pentenolide (**11**) without stereomutation. Subsequent thermal lactone opening is followed by loss of stereochemical integrity of the conjugated 2 4-bonds and methods for the control of this unwanted reaction are being investigated.

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‡ The geometry of the eight isomers of (**12**) was demonstrated by analysis of their ^{13}C and ^{1}H n.m.r. spectra and details will be reported in a full paper.

[1] M. J. Begley, L. Crombie, R. W. King, D. A. Slack, and D. A. Whiting, *J.C.S. Perkin I*, 1977, 2393, and refs. cited therein.
[2] D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1973, 582.
[3] M. J. Begley, L. Crombie, D. A. Slack, and D. A. Whiting, *J.C.S. Perkin I*, 1977, 2402.
[4] C. E. Berkoff and L. Crombie, *J. Chem. Soc.*, 1960, 3734.