The Oxidative Rearrangement of Chalcones by Thallic Acetate: a Chemical Analogy for Isoflavone Biosynthesis

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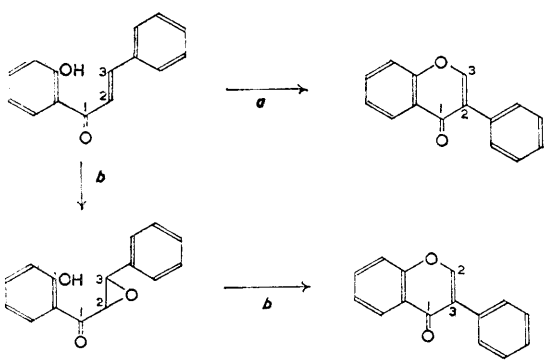
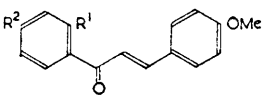
THE biosynthesis of isoflavonoids from chalcone precursors has been shown[1] to involve a 1,2-aryl migration (Scheme 1, route *a*). There is no chemical analogy for this process as the boron trifluoride-promoted rearrangement of chalcone epoxides leading to isoflavones involves a 1,2-aroyl shift[2] (Scheme 1, route *b*). We report that reaction between thallic acetate and chalcones gives intermediates leading to isoflavones. This reaction is formally similar to the biosynthetic process, since it is an oxidative transformation associated with a 1,2-aryl migration. This new synthesis of isoflavones, which involves a chalcone rather than a flavanone precursor, demonstrates the mechanistic possibility of the direct utilisation of chalcones[3] rather than flavanones[4] in isoflavone biosynthesis.

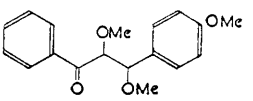


SCHEME 1. The inter-aryl C_3 unit is numbered to indicate the observed mode of skeletal rearrangement in the two processes.

The reaction of 4-methoxychalcone (I) with thallic acetate in boiling methanol (100 hr.) gave a ketone (ν_{max} 1680 cm.$^{-1}$), $C_{18}H_{20}O_4$, m.p. 83°, with n.m.r. spectrum that indicated the presence of a benzoyl group, a *p*-methoxyphenyl group, a CH–CH grouping [τ 4·93 (d, 1H), 5·20 (d, 1H), AB system, J_{AB} 8 c./sec.], and two methoxy-groups. This suggested that the product was either the 1,3-diaryl-2,3-dimethoxypropan-1-one (II) or the 1,2-diaryl-3,3-dimethoxypropan-1-one (III). The constitution (III) was shown to be correct by synthesis. Boron trifluoride-catalysed rearrangement of the epoxide of chalcone (I) gave the keto-aldehyde (IV), isolated as its copper complex, which reacted with methanolic hydrogen chloride to give the acetal (III).

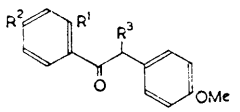


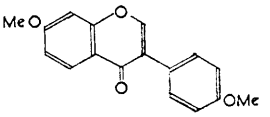
(I) $R^1 = R^2 = H$



(II)

(V) $R^1 = OCH_2Ph$, $R^2 = OMe$
(XII) $R^1 = OH$, $R^2 = OMe$





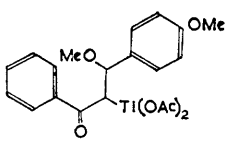
(III) $R^1 = R^2 = H$, $R^3 = CH(OMe)_2$ (VII)
(IV) $R^1 = R^2 = H$, $R^3 = CHO$
(VI) $R^1 = OCH_2Ph$, $R^2 = OMe$, $R^3 = CH(OMe)_2$
(X) $R^1 = OH$, $R^2 = OMe$, $R^3 = Me$
(XIV) $R^1 = OH$, $R^2 = OMe$, $R^3 = CH(OMe)_2$

The thallic acetate oxidation of 2′-benzyloxy-4,4′-dimethoxychalcone (V) in methanol solution gave the acetal (VI), 47%, m.p. 113°, which by consecutive hydrogenolysis (Pd–C in ethyl acetate) and hydrolysis (ethanolic hydrochloric acid) gave 7,4′-dimethoxyisoflavone (VII) (44%). The formation of an isoflavone by this reaction sequence proves the occurrence of a skeletal rearrangement, and exemplifies a new general synthetic route from chalcones to isoflavones.

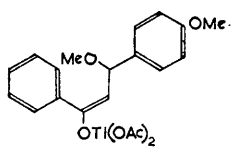
The rearrangement of 4-methoxychalcone (I) was repeated with material labelled with ^{14}C at C(α) (Scheme 2). The radioactivity in the chalcone (I) and in the rearrangement product (III) was shown to be specifically located at the starred carbon atoms by the degradation shown in Scheme 2. These results prove that the thallic acetate-promoted rearrangement of the chalcone involves exclusively 1,2-aryl migration. It was also shown (Scheme 2), in agreement with previous studies,[2] that the acetal (III) obtained by rearrangement of the epoxide of the radioactive chalcone (I) was exclusively labelled at the carbon atom of the acetal group, thus confirming that this alternative mode of skeletal rearrangement involves only 1,2-aroyl migration.

Two mechanisms may be envisaged for the thallic acetate-promoted rearrangement. One involves alkoxythallation[5,6] of the double bond of the chalcone to give an intermediate (VIII) which then rearranges. The alternative involves the formation, followed by rearrangement, of an intermediate organothallium derivative (IX). The latter is more acceptable on general mechanistic grounds as it does not involve the development of carbonium-ion character adjacent to a carbonyl group. Some evidence that ketones may react with thallic acetate by way of an intermediate enol thallium derivative (*cf.* ref. 7) comes from the following observations. The oxidation of angolensin methyl ether (X) with thallic acetate yields the coumaranone (XI), and the oxidation of 2′-hydroxy-4,4′-dimethoxychalcone (XII) gives, in addition to the corresponding flavanone and flavone, the coumaranone (XIII) which is believed to arise by oxidation of the intermediate deoxybenzoin acetal (XIV). These oxidative cyclisations of *o*-hydroxydeoxybenzoins could well involve intermediate organothallium derivatives of the corresponding enols. The structure of the coumaranone (XIII) follows from its spectroscopic properties and from its reduction by sodium borohydride to an alcohol, which undergoes acid-catalysed hydrolysis and elimination of formic acid to give the benzofuran derivative (XV).

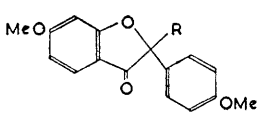
Although it is recognised that oxidation by thallic acetate is a remote model for the biosynthesis of isoflavones from chalcones, the general



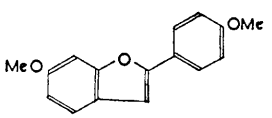
(VIII)



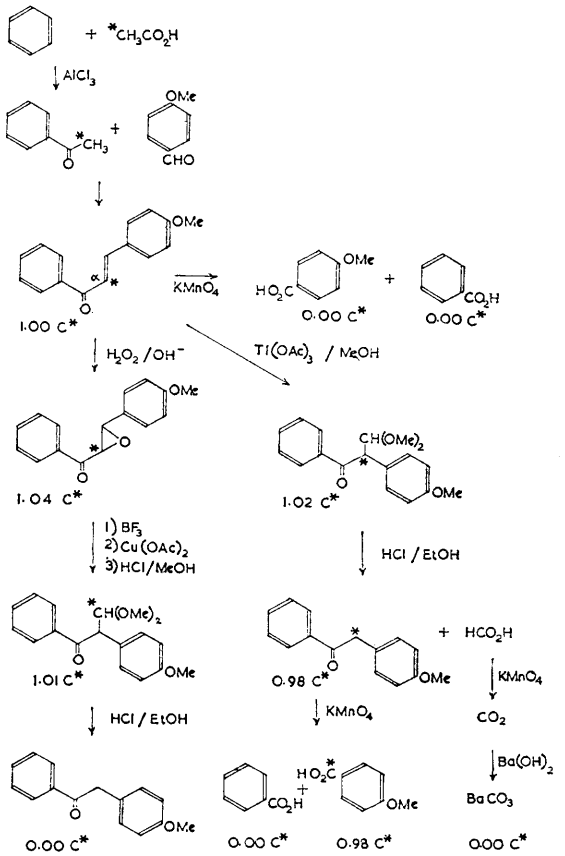
(IX)



(XI) R = Me
(XIII) R = $CH(OMe)_2$



(XV)



SCHEME 2. The figures under the formulae refer to the specific activities of the compounds relative to 4-methoxychalcone.

features of both oxidative processes could correspond. In comparison with other oxidants,[6] the use of thallic acetate has been little studied. The several types of reaction now reported for thallic acetate indicate a number of general applications and illustrate the pronounced reactivity[6] of organothallium intermediates which give products by heterolysis of carbon–thallium or oxygen–thallium bonds.

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[1] For reviews see H. Grisebach and W. D. Ollis, *Experientia*, 1961, **11**, 4; H. Grisebach, "Chemistry and Biochemistry, of Plant Pigments," ed. T. W. Goodwin, Academic Press, London, 1965, 279.
[2] H. O. House, *J. Amer. Chem. Soc.*, 1956, **78**, 2298; H. O. House and G. D. Ryerson, *ibid.*, 1961, **83**, 979; H. Grisebach and W. Barz, *Chem. Ber.*, 1964, **97**, 1688.
[3] E. Wong, *Chem. Comm.*, 1968, 395.
[4] L. Patschke, W. Barz, and H. Grisebach, *Z. Naturforsch.*, 1966, **21b**, 201; H. Grisebach and W. Bilhuber, *ibid.* 1967, **22b**, 747; E. Moustafa and E. Wong, *Phytochemistry*, 1967, **6**, 625.
[5] H. J. Kabbe, *Annalen*, 1962, **656**, 204; C. B. Anderson and S. Winstein, *J. Org. Chem.*, 1963, **28**, 605; K. C. Pande and S. Winstein, *Tetrahedron Letters*, 1964, 3393; J. B. Lee and M. J. Price, *Tetrahedron*, 1964, **20**, 1017; P. M. Henry, *J. Amer. Chem. Soc.*, 1965, **87**, 990, 4423; 1966, **88**, 1597; J. K. Kochi and T. W. Bethea, *J. Org. Chem.*, 1968, **33**, 75.
[6] W. Kitching, *Organometallic Chem. Rev.*, 1968, **3**, 61.
[7] G. W. K. Cavill and D. M. Solomon, *J. Chem. Soc.*, 1955, 4426.