Regiospecificity of Phenol Chromenylation

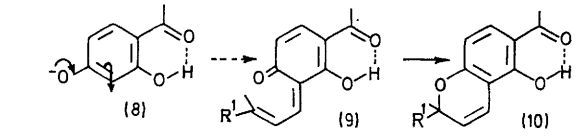
By DAVID G. CLARKE, LESLIE CROMBIE,* and DONALD A. WHITING*
(*Department of Chemistry, The University, Nottingham* NG7 2RD)

Summary Proposals are made which account for the regiospecificity observed in the pyridine-catalysed reaction between certain aldehydes and phenols; they can be extended to other situations.

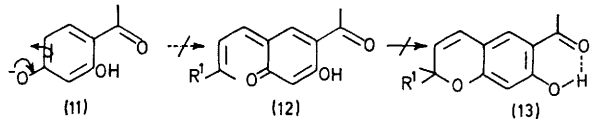
THE reaction between citral and appropriate phenols, under pyridine catalysis, leads to chromens and 1,3,8-axially bridged *p*-menthanes, and was first reported in connexion with the synthesis of deoxybruceol (**1**).[1a] It has since found considerable application in the synthesis of natural compounds, and has been extended to a range of phenols, together with α-unsaturated aldehydes or acetals (or their hydrated counterparts).[1,2] The reaction is frequently highly regiospecific and consideration of existing data leads us to propose that the stability of the transition state leading to the dienone intermediate is a major factor in

determining the orientation of chromenylation once the triggering phenolate anion is formed. Relative acidities of phenol groups are of importance in selection of the latter feature.

In a simple case (**2**; R^1 = OH) → (**6**; R^1 = OH) only one chromen is possible, but with R^1 = n-pentyl, two chromens (**6**) and (**7**) are formed (together with other chromen-derived products) and the reaction is not regiospecific.[1] With 2,4-dihydroxyacetophenone, important regioselecting factors come into play. As already pointed out elsewhere,[2a,c] chromenylation is triggered by the acidic, unchelated hydroxy-group, and 'citrylidene' formation is inhibited by chelation of the second hydroxy-group. A choice of site still remains for chromenylation. Orientation A allows retention of the stabilisation energy of the chelate system in the dienone forming reaction: in B it is lost. Chromen (**10**) is the product when $R^1 = Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2-$ (84% yield), H (75%), or Me (59%);[2] no isomeric (**13**) was found. Use of the acetals (**14**) in the pyridine-catalysed reaction leads regiospecifically to (**10**), *via* (**16**), with



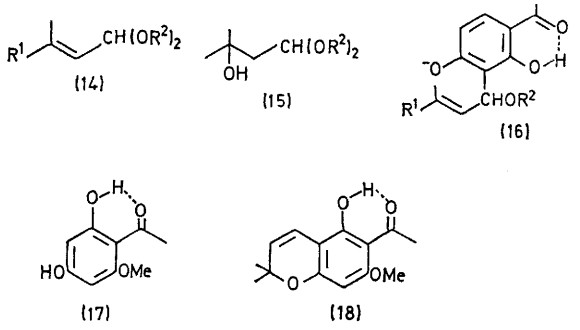
Orientation A



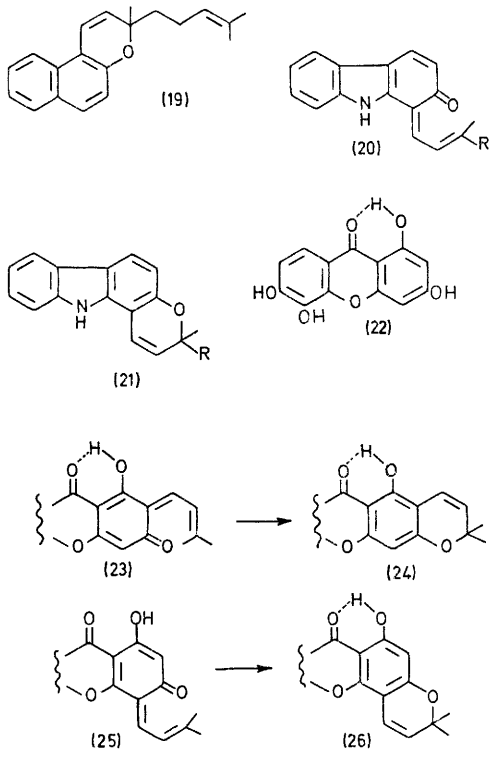
Orientation B

$R^1 = Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2-$ (88%) or Me (60%), and similar regiospecificity is found with the hydrated acetal (**15**) which gives (**10**; R^1 = Me).[2b,d] A related case is chromenylation of (**17**) by (**15**) which gives (**18**) (68%) and not the isomer;† other examples accord with this view.[2b,d,3]

In a further group of chromenylations, retention of the delocalisation energy of a fused ring during formation of the dienone intermediate governs the regiospecificity. On analysis, this factor will be found to be implicit in the formation of only natural (**1**), and not its isomer, in the deoxybruceol synthesis;[1] here the coumarin ring controls the situation. Simpler examples are the chromenylation of 2-naphthol at the 1-position only, giving (**19**), and the chromenylation of 3-hydroxycarbazole at position 2 giving (**21**) *via* (**20**), and not the 4-isomer.

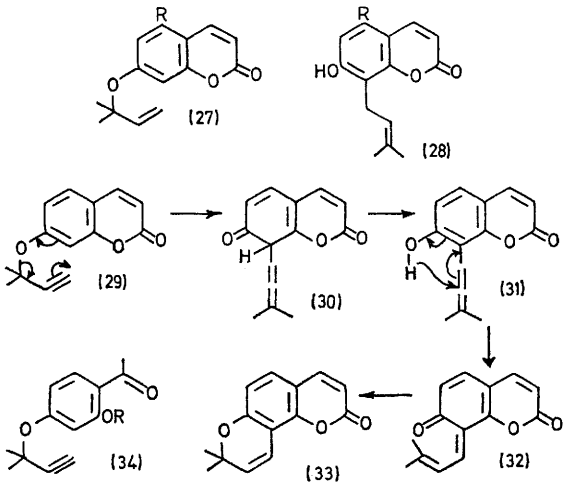


In more complex systems two potentially controlling features may conflict and it is in such systems that mixtures of chromens have been found. Thus the chromenylation of (**22**), initiated by the 3-hydroxy-group, can lead to dienone (**23**) with loss of 4-pyrone delocalisation, and hence to (**24**);



or to (**25**) with loss of chelate stabilisation and hence to (**26**). Experimentally both (**24**; jacareubin) and (**26**) are formed.[2b,d] The 1,3,5- and 1,3,7-trihydroxyxanthones[5] and 1,3-dihydroxyacridones[2b] provide further illustration of the diminished regiospecificity with both linear and angular

† A useful indicator[4] of the ability of a phenol to chromenylate, and its regiospecificity, is provided by heating (88°; 1 h) in [$^2H_5$]pyridine–D_2O in an n.m.r. tube, followed by survey of the aromatic proton exchange [diluting with $(D_3C)_2CO$ as necessary].



products being formed. In some cases, however, one energetic factor may be dominant, *e.g.* chromenylation of 2-methyl-5,7-dihydroxychromone.[2a,c]

The considerations discussed above appear to be germane to regiospecificity in certain other phenol reactions. Thus Claisen rearrangement of (**27**; R = OMe) gives (**28**; R = OMe) exclusively, whilst (**27**; R = H) gives (**28**; R = H) (74%, along with 14% of 6-isomer).[6] The acetylene (**29**) gives (**33**) with no linear isomer,[7] presumably by the mechanism shown.[8] An illuminating case is (**34**) which, when R = H, gives only (**10**; R^1 = Me): when the chelated hydroxy-group is blocked by acetylation, the effect ascribable to bond fixation is lost and both the acetates of (**10**; R^1 = Me) and (**13**; R^1 = Me) are formed.[9] Further examples fall into line.[10]

(*Received*, 30*th May* 1973; *Com.* 773.)

[1] (a) L. Crombie and R. Ponsford, *Chem. Comm.*, 1968, 368; (*b*) *ibid.*, p. 894; (c) *Tetrahedron Letters*, 1968, 4557; (d) *J. Chem. Soc.* (*C*), 1971, 788; (e) *ibid.*, p. 796.
[2] (a) W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *Chem. Comm.*, 1969, 58; *ibid.*, p. 970; (c) *J. Chem. Soc.* (*C*), 1971, 804, 811.
[3] W. J. Donnelly and P. V. R. Shannon, *Chem. Comm.*, 1971, 76.
[4] E. S. Hand and R. M. Horowitz, *J. Amer. Chem. Soc.*, 1964, **86**, 2084.
[5] J. R. Lewis and J. B. Reary, *J. Chem. Soc.* (*C*), 1970, 1662.
[6] R. D. H. Murray, M. M. Ballantyne, and K. P. Mathai, *Tetrahedron*, 1971, **27**, 1247; R. D. H. Murray, T. C. Hogg, M. M. Ballantyne, and P. H. McCabe, *Tetrahedron Letters*, 1971, 3317.
[7] J. Hlubucek, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1971, 2347.
[8] J. Zsindely and H. Schmid, *Helv. Chim. Acta*, 1968, **57**, 1510; R. Hug, H.-J. Hanson and H. Schmid, *Chimia* (*Switz*), 1969, **23**, 108.
[9] F. Bohlmann and U. Bühmann, *Chem. Ber.*, 1972, **105**, 863.
[10] S. K. Mukerjee, S. C. Sarkar, and T. R. Seshadri, *Indian J. Chem.*, 1972, **10**, 374; A. C. Jain and M. K. Zutshi, *Tetrahedron Letters*, 1971, 3179.