Conversion of Phenols into Chromens: Regiospecificity and Scope

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Regiospecificity of the pyridine-catalysed reaction of α-unsaturated aldehydes or acetals with phenols is discussed. It is proposed that, after selection of the acidic triggering hydroxy-group, retention of the delocalisation energy of attachments to the phenol plays an important part in deciding which *o*-quinone methide, and hence which chromen, ' citrylidene ' type, or cyclol will form. Examples involving chelated systems and fused homo- and hetero-cyclic aromatic rings are illustrated, and pyridine-catalysed deuteriation is shown to be a useful indicator of the ability of a phenol to undergo conversion into a chromen, and of the position at which pyran formation occurs. Certain rearrangements of the Claisen type appear to follow an orientation pattern explicable in terms of similar considerations. In some systems, where requirements for retention of the delocalisation energy from two features conflict, both possible products are formed. When terminally unhindered reagents such as acrylaldehyde acetal or methyl vinyl ketone are employed, products from *C*-Michael addition by the phenol are found. Some experimental conditions influencing chromen formation are mentioned.

PYRIDINE-CATALYSED reaction between citral and phenols [1] has been developed as a flexible synthetic method applicable to a range of natural products including cannabinoids,[2,3] prenylated coumarins,[1,4,5] chalcones,[6] xanthones,[7] and acridone and carbazole alkaloids.[8] The synthetic objective is frequently the chromen [*e.g.* (5)], but may be the ' citrylidene ' type (8) or the ' cyclol ' (9).[2,9] Sometimes sets of natural meroterpenoids containing members with structures related to (5), (8), and (9) occur together in a plant, as in *Cannabis sativa*,[10] *Eriostemon brucei*,[11] and *Murraya koenigii*.[8]

As a result of work described here and in our earlier papers the reaction seems best expressed as in Scheme 1. The natural precursors in Scheme 1 are possibly the

[1] L. Crombie and R. Ponsford, *Chem. Comm.*, 1968, 368; *Tetrahedron Letters*, 1968, **43**, 557; *cf.* C. E. Berkoff and L. Crombie, *J. Chem. Soc.*, 1960, 3734.

[2] L. Crombie and R. Ponsford, *Chem. Comm.*, 1968, 894; *J. Chem. Soc.* (*C*), 1971, 794.

[3] V. V. Kane and R. K. Razdan, *J. Amer. Chem. Soc.*, 1968, **90**, 6551.

[4] L. Crombie and R. Ponsford, *J. Chem. Soc.* (*C*), 1971, 788.

[5] D. E. Games and N. J. Haskins, *Chem. Comm.*, 1971, 1005.

[6] W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *Chem. Comm.*, 1969, 58; *J. Chem. Soc.* (*C*), 1971, 804.

[7] W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *Chem. Comm.*, 1969, 970; *J. Chem. Soc.* (*C*), 1971, 811.

[8] W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, preceding paper, and references cited there.

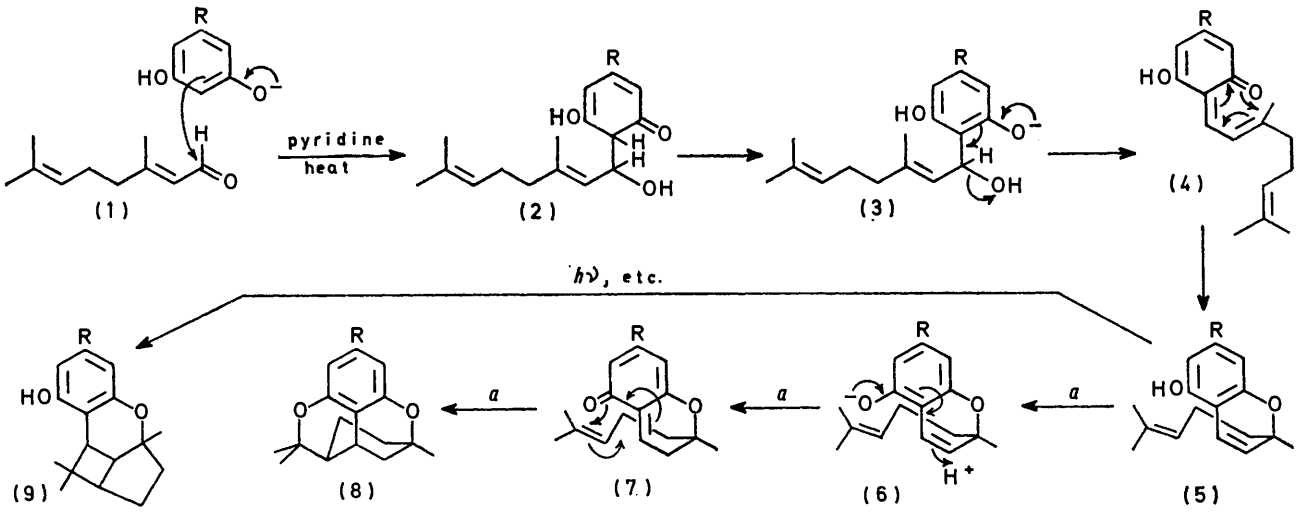
[9] L. Crombie, R. Ponsford, A. Shani, B. Yagnitinsky, and R. Mechoulam, *Tetrahedron Letters*, 1968, 5771.

[10] Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, 1971, **93**, 217; R. Mechoulam, *Science*, 1970, **168**, 1159; R. Mechoulam and Y. Gaoni, *Fortschr. Chem. org. Naturstoffe*, 1967, **25**, 174.

[11] A. M. Duffield, P. R. Jefferies, E. N. Maslem, and A. I. M. Roe, *Tetrahedron*, 1963, **19**, 593; P. R. Jefferies and G. K. Worth, *ibid.*, 1973, **29**, 903.

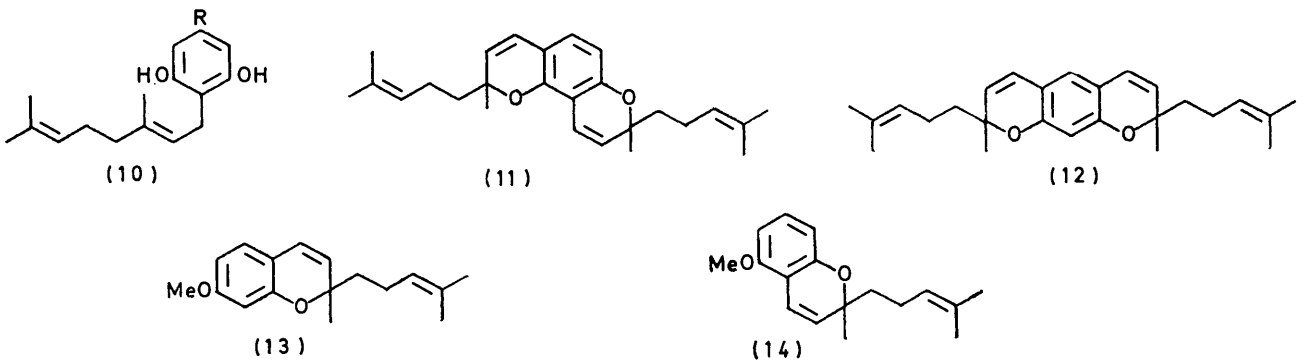
prenylated compounds (10) which in some cases co-occur, *e.g.* cannabigerol[11] and heptaphylline[12,13] with the other meroterpenoids. Such natural precursors are at a different oxidation state from compounds in this Scheme and it is likely that the *o*-quinone allylide structure (4) is reached by 1′-hydride transfer and proton loss.[10] In the biomimetic synthesis the correct oxidation state is present at the outset as an α-unsaturated aldehyde is employed.

The present paper treats the scope, regiospecificity, and mechanism of chromen formation.



SCHEME 1

[a] The mechanism will be discussed more fully in a later paper.



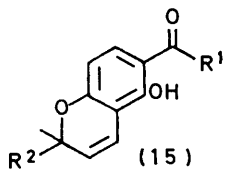
Since the reaction involves *C*-hydroxyalkenylation of a phenolate anion, it is to be expected that a *meta*-dihydric arrangement would facilitate reaction. Indeed, phenol, quinol, and catechol all fail to react with citral in pyridine (120 h; 160°). Resorcinol reacts with the same reagents (24 h; 140°) to yield the angular (11) and linear (12) benzodipyrans. Formation of the two possible chromens, together with the benzodipyran (11) has been mentioned, but no details were given.[14] Chromen formation is still possible if one hydroxy-group of resorcinol is blocked. Thus 3-hydroxyanisole affords the chromens (13) and (14) in poor yield: these are readily distinguishable by ^{1}H n.m.r. (1,2,4- and 1,2,3-substitution).

Chromen formation from resorcinol, and from its monomethyl ether, is not markedly regiospecific. In contrast, we showed earlier that resacetophenone, and ω-methoxyresacetophenone, form chromens regiospecifically with citral or 3-methylcrotonaldehyde (or an equivalent); the products are of type (15). In these cases, and others involving chelated hydroxy-groups, only the more acidic non-chelated hydroxy-groups are involved in chromen formation, or the ensuing formation of a citrylidene type. Other workers[15,16] have since claimed the involvement of chelated hydroxy-groups in such reactions, since the chromen (17) was obtained from phloroacetophenone,[15] and the chromen (18) and the 'citrylidene' (19) were also obtained from this phenol.[16] The argument seems fallacious as it implies that in a 2′,6′-dihydroxyacetophenone type both hydroxy-groups are simultaneously chelated with the carbonyl. In fact, phloroacetophenone (20) has two equivalent structures in rapid equilibrium. It is

[12] Y. Gaoni and R. Mechoulam, *Chem. Comm.*, 1964, 82.
[13] B. S. Joshi, V. N. Kamat, D. H. Gavad, and T. R. Govindachari, *Phytochemistry*, 1972, **11**, 2065.
[14] V. V. Kane and R. K. Razdan, *Tetrahedron Letters*, 1969, 591.
[15] W. J. G. Donnelly and P. V. R. Shannon, *Chem. Comm.*, 1971, 1876; *J.C.S. Perkin II*, 1972, 25.
[16] V. V. Kane and T. L. Grayeck, *Tetrahedron Letters*, 1971, 3991.

notable in this connection that 2',6'-dihydroxyacetophenone readily affords the chromen (21) with citral and pyridine, but benzodipyran formation was not observed. The formation of (22) from 2',4',5'-trihydroxyacetophenone and citral can also be explained in terms of triggering by the anion derived from the most acidic of the three hydroxy-groups.[6]

The specificity of chromen formation from resacetophenone and ω-methoxyresacetophenone is not confined to selection of the hydroxy-group whose ionisation triggers the reaction, but extends to regiospecificity since



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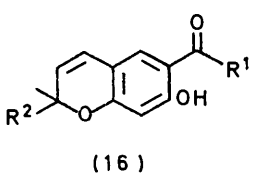

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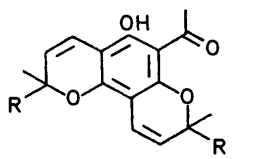
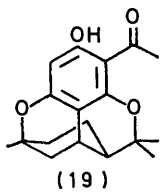


(17) R = Me

(18) R =



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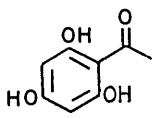
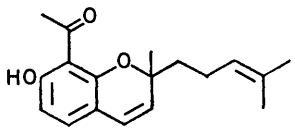


(20)

in both examples ' angular ' chromens of type (15) are the only products isolated: linear isomers (16) have not been found. This may be rationalised in terms of the anion (23) ⟷ (23a) ⟷ (23b) formed in pyridine. Resonance contributor (23b), retaining the stabilisation energy of the chelate ring is likely to be more important than (23a) where the ring is disrupted. The transition state leading to hydroxyalkenylation at C-3 is thus expected to be of lower energy than that leading to



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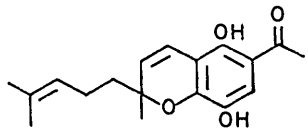

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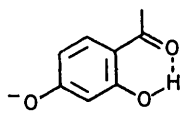

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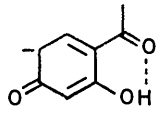
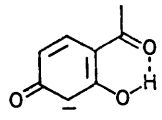
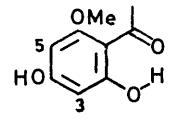


(23a)



(23b)



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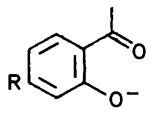

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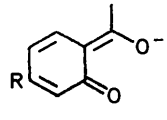
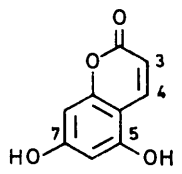


(25a)

reaction at C-5. Similar factors then apply to the irreversible dehydration step, *cf.* (3) ⟶ (4), leading to the enone precursor of the chromen. Such control is found in chromen formation from other acylphenols, *e.g.* (24), which are attacked at C-3, not C-5. It is worthy of note that in an ionised *o*-acetylphenol the bond fixation effect still applies, and the charge localised on aromatic carbon atoms will be limited by the importance of the delocalisation (25) ⟷ (25a).

Regiospecificity is also found in the formation of benzodipyrans from coumarins. Thus 5,7-dihydroxycoumarin (26) reacts with citral and pyridine to give a mixture of the two benzodipyrans (27) and (28),



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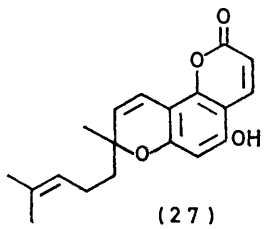

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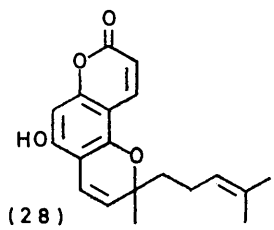

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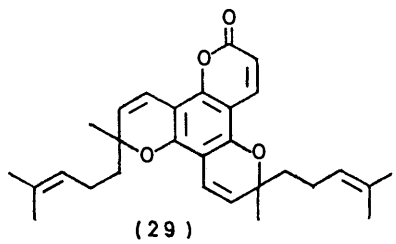

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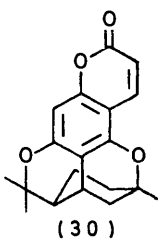

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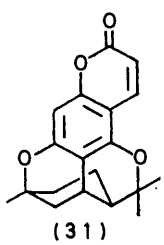

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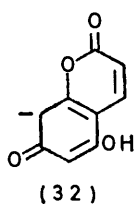

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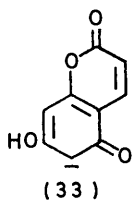

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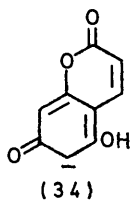
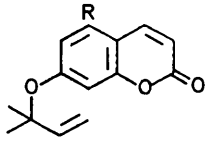


(34)

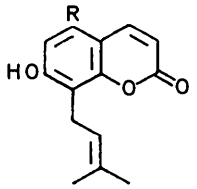
together with the benzotripyran (29).[1,4] Further heating of (28) in pyridine gives deoxybruceol (30),[17] which can also be obtained directly from the first reaction

[17] L. Crombie and D. A. Slack, unpublished work.

mixture if heating is continued. It thus becomes clear why, in our original synthesis, the compound (31), with



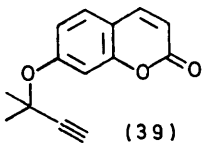
(35) R = OMe
(37) R = H



(36) R = OMe
(38) R = H

' unnatural ' orientation, could not, despite a search, be found.[1,4] These facts may be rationalised in terms of bond fixation leading to preferred stability in transition states from anionic intermediates involving contributors such as (32) and (33), rather than (34) which does not retain the pyrone stabilisation energy. The pattern of reaction of 5,7-dihydroxy-4-phenylcoumarins (with 3-hydroxy-3-methylbutyraldehyde dimethyl acetal in pyridine) can be similarly explained.[5]

There is evidence in the literature which suggests that related factors play a significant part in determining the regiospecificity of reactions involving Claisen rearrangements.[18] Thus the coumarin (35) gives (36) exclusively and (37) gives 74% of (38) along with 14% of the 6-isomer.[19a,b] The acetylenic coumarin (39) gives (40) with no linear isomer,[20] presumably by the mechanism shown.[21] An illuminating case is (41) which gives only (42); when the chelated feature is disrupted by acetylation, as in (43), the effect ascribable to bond fixation is lost and both (44) and (45) are formed.[22] Further examples which support this view of the origins of the regiospecificity can be cited.[23]



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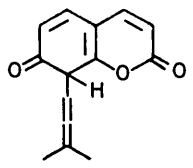

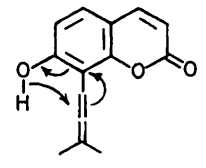

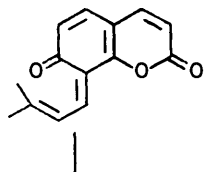

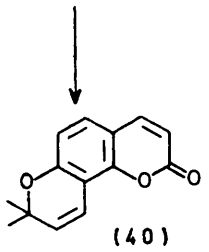

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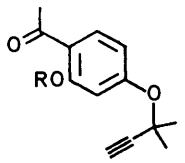
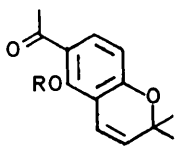
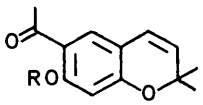


(41) R = H
(43) R = Ac

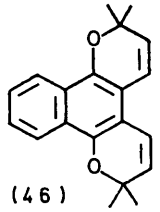


(42) R = H
(44) R = Ac



(45) R = Ac

The foregoing examples involve *m*-dihydric phenols. The only phenol not of this type which has hitherto been shown to undergo pyridine-catalysed chromen formation by our method is 1,4-dihydroxynaphthalene, which gives the naphthodipyran (46) on treatment with 3-hydroxyisovaleraldehyde dimethyl acetal.[7] This showed the carbanion (47) to be responsive to hydroxyalkenylation and the subsequent mechanistic steps, and encouraged further investigation. 1-Naphthol, 2-naphthol, 2,3-dihydroxynaphthalene, and 2,7-dihydroxynaphthalene all gave naphthopyrans with citral in pyridine, though yields were poor. 1-Naphthol formed (48) without structural ambiguity. 2-Naphthol provided only the naphthopyran (49), showing the importance of delocalisation giving carbanionic character at C-1 (50) relative to C-3 (51) in which the aromatic character of the residual ring is disrupted. As expected 2,3-dihydroxynaphthalene gave the naphthopyran (52),



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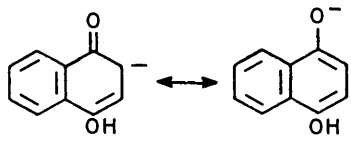

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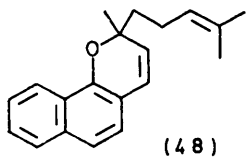
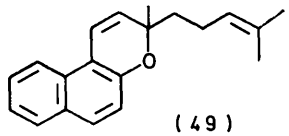


(48)



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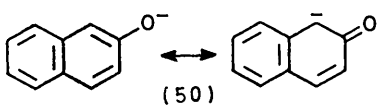

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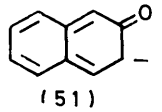
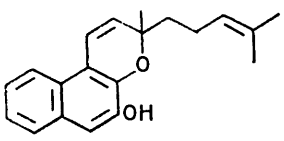


(51)

[18] D. S. Tarbell, *Org. Reactions*, 1944, **2**, 1; W. Baker and O. M. Lothian, *J. Chem. Soc.*, 1935, 628; 1936, 274.
[19] (*a*) R. D. H. Murray, M. M. Ballantyne, and K. P. Mathai, *Tetrahedron*, 1971, **27**, 1247; (*b*) R. D. H. Murray, T. C. Hogg, M. M. Ballantyne, and P. H. McCabe, *Tetrahedron Letters*, 1971, 3317.
[20] J. Hlubucek, E. Ritchie, and W. Taylor, *Austral. J. Chem.*, 1971, 2347.
[21] J. Zsindely and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 1510; R. Hug, H.-J. Hanson, and H. Schmid, *Chimia (Switz.)*, 1964, **23**, 108.
[22] F. Bohlmann and U. Bühmann, *Chem. Ber.*, 1972, **105**, 863.
[23] 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.

together with the symmetrical naphthodipyran. Similarly 2,7-dihydroxynaphthalene gave (53) and a correspondong symmetrical naphthodipyran.

A useful indicator of the ability of a phenol to undergo chromen formation, and of the regiospecificity, is given by deuterium exchange.[24] The phenol (50 mg) was heated with [$^2H_5$]pyridine (100 μl) and D_2O (200 μl) in an n.m.r. tube for 1 h at 88°, and, after dilution with



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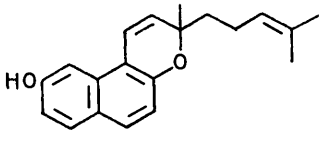


(53)

deuterioacetone as necessary, the aromatic proton exchange was surveyed. Some results are given in the Table. We have not succeeded in forming chromens

Pyridine-catalysed deuterium exchange in phenols

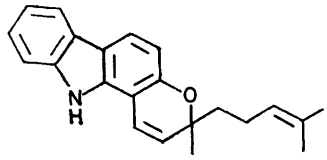
Phenol	Aromatic exchange (%)	Acetyl exchange (%)
1,3-Dihydroxybenzene	80 (2,3,6) [a]	
2′,4′-Dihydroxyacetophenone	70 (3′)	25
2′,5′-Dihydroxyacetophenone	Nil [b]	80
2′,6′-Dihydroxyacetophenone	95 (3′,5′)	50
3′-Hydroxyacetophenone	Nil [b]	40
2′,4′,6′-Trihydroxyacetophenone	100 (3′,5′)	N.d. [c]
3-Methoxyphenol	12	
2′,3′,4′-Trihydroxyacetophenone	Nil [b]	85
Phenol	Nil [b]	
1,2-Dihydroxy-4-nitrobenzene	Nil [b]	
3,4-Dihydroxycinnamic acid	Nil [b]	
1-Naphthol	100 (2)	
2-Naphthol	100 (1)	
2,3-Dihydroxynaphthalene	100 (1,4)	
2,7-Dihydroxynaphthalene	100 (1,8)	

[a] Position of deuterium exchange. [b] Attempted chromen formation (pyridine catalysis) failed. [c] Not determined.

from phenols which do not show aromatic exchange. Those showing exchange are attacked at the positions indicated by deuteriation, in varying yields.

Further regiospecific chromen-forming reactions which may be explained in the manner discussed are exemplified by the reaction of 2-hydroxycarbazole with citral and pyridine [8] which gives only the chromen (54), preserving the aromatic character of the indole nucleus in transition states leading to the product. Further similar cases can be cited, but some involve additional complication. Thus the reaction of pinocembrin (55) with citral and pyridine provides an excellent synthesis of the natural product rubranine (56).[6] Interruption of the reaction gives evidence of both benzodipyrans (57) and (58), showing that anions of (59), the product of base-cataysed dihydropyrone opening which can close in either sense, are present. A subsequent synthesis [16] * involves condensation of (19) with benzaldehyde and is effectively a re-ordering of the steps.

In more complex molecules, the factors controlling regiospecificity may be in competition and mixtures of chromens may be obtained. Thus 1,3,5- and 1,3,7-trihydroxyxanthones [26] and 1,3,5,6-tetrahydroxyxanthones [7] each give mixtures of linear (60)—(62) and



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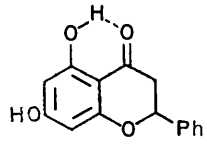

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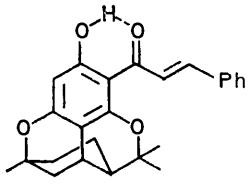

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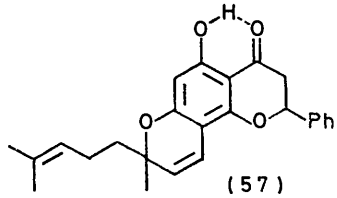

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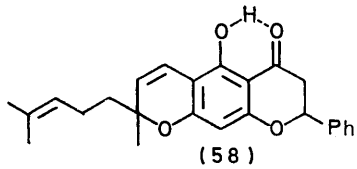

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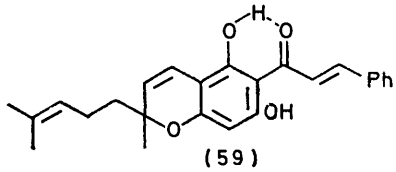
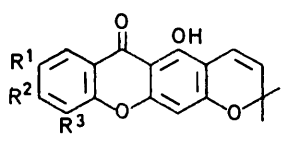
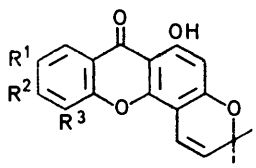


(59)

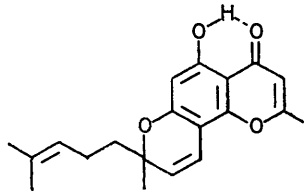
angular (63)—(65) chromens. Chromen formation is, in all these cases, initiated by an acidic hydroxy-group, but



(60) $R^1 = R^2 = H, R^3 = OH$
(61) $R^2 = R^3 = H, R^1 = OH$
(62) $R^1 = H, R^2 = R^3 = OH$



(63) $R^1 = R^2 = H, R^3 = OH$
(64) $R^2 = R^3 = H, R^1 = OH$
(65) $R^1 = H, R^2 = R^3 = OH$



(66)

the transition states leading to linear chromen formation allow retention of the chelate stabilisation with loss of

* Actually this approach was first reported by Combes *et al.*[25]

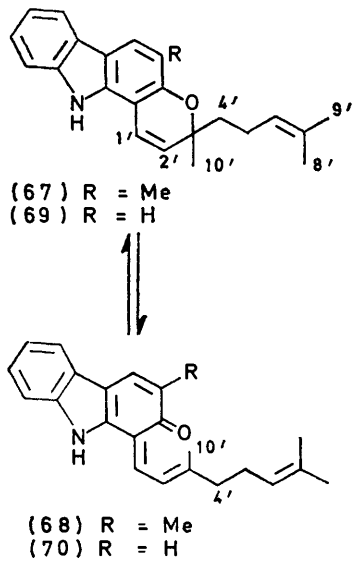
[24] E. S. Hand and R. M. Horowitz, *J. Amer. Chem. Soc.*, 1964, **86**, 2084.

[25] G. Combes, P. Vassort, and F. Winternitz, *Tetrahedron*, 1970, **26**, 5981; *cf.* G. Combes, J.-L. Montero, and F. Winternitz, *Compt. rend.*, 1972, **274**, 1313.

[26] J. R. Lewis and J. B. Reary, *J. Chem. Soc.* (*C*), 1970, 1662.

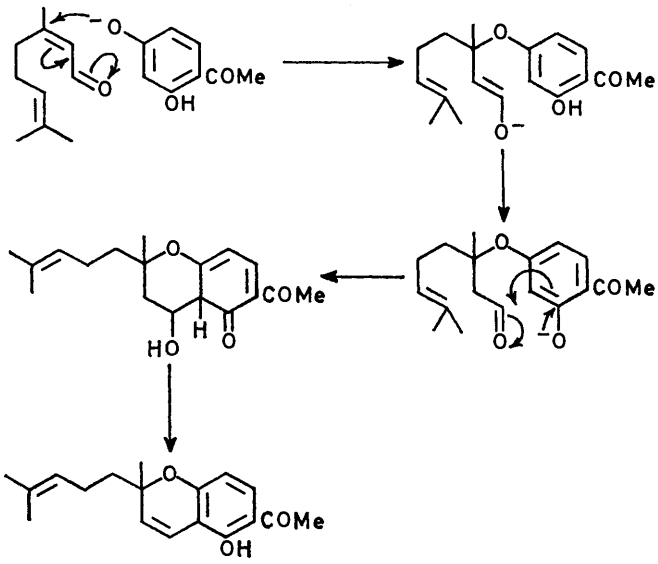
pyrone resonance, whilst those leading to angular chromens allow loss of the former but retention of the latter. The energetics of the two modes of reaction permit competitive formation of both products in some cases. Thus chromen formation from 1,3-dihydroxyacridone also gives a mixture of linear and angular chromens.[7,8] On the other hand, 2-methyl-5,7-dihydroxychromone gave mainly the angular benzodipyran (66), retention of pyrone resonance apparently being more important.[6]

The first stage of Scheme 1 is reversible. When acetals are used this addition step becomes a displacement step leading to the ether of (2). Stage (3) ⟶ (4) is essentially irreversible under the conditions of the reaction and the enone–chromen step (4) ⇌ (5) is regarded as a reversible electrocyclic reaction. In this connection, natural mahanimbine (67), m.p. 91—92°, $[\alpha]_D^{24}$ +45·4° (*c* 4·9 in toluene), was heated in iso-octane at 90° in the dark and the solution was monitored by o.r.d. at intervals. Racemisation of mahanimbine ensued with a half-racemisation time of 1½—2 days, which is readily explained by electrocyclic opening to the enone (68). Preparatively, (±)-mahanimbine, m.p. 73—74°, may be obtained by distillation of (+)-mahanimbine:[27] similar racemisation may well explain why certain natural chromens, *e.g.* cannabichromen[12] have only been isolated in racemic form. Further evidence for the equilibrium comes from heating normahanimbine (69) in pyridine and D_2O at 150°. By using n.m.r. analysis, it was observed that deuterium was substantially incorporated into the non-terminal



methyl (10′) (44% after 4 days) and also into the 4′-CH_2 (17%). Incorporation into these positions can be explained by invoking anion formation by the enone (70). Chromen–tetraenone interconversions, both heat- and light-catalysed, are well documented.[28]

Kane and Grayeck[16] have proposed a mechanism (Scheme 2) for chromen formation which is said to



SCHEME 2

account for the regiospecificity. It involves an *O*-Michael reaction, and ring closure is initiated by the second hydroxy-group. Such a mechanism presents a number of difficulties, among them the *O*-Michael step, its inapplicability to naphthols, the need to invoke the anion of the chelated hydroxy-group of resacetophenone in an unfavourable way, *etc.* In addition it does not account for regiospecificity as discussed above.

The unsaturated aldehydes phytal,[6] farnesal,[6] citral,[1,2,4,6] cinnamaldehyde,[7] 3-methylcrotonaldehyde,[7] and crotonaldehyde[7] have all been shown to give chromens on heating with suitable phenols and pyridine.* The dimethyl acetals of citral and 3-methylcrotonaldehyde can be used with the advantage of increased stability in pyridine.[7] 4,4-Dimethoxy-2-methylbutan-2-ol (71) has been developed as an easily available reagent to replace 3-methylcrotonaldehyde in dimethylchromen formation.[7] Further reagents have now been examined in an effort to expand the synthetic scope.

Aldol dimethyl acetal (72) reacted with resacetophenone in pyridine at 120° in 24 h to give (73) in poor yield, identical with a specimen prepared from crotonaldehyde. Acrylaldehyde polymerised rapidly in hot pyridine[7] but its diethyl acetal, on heating with reacetophenone in pyridine (110°; 20 h) gave two products.

* Attention is drawn to certain other base-catalysed reactions which involve hydroxyalkenylation and may be mechanisitically related. These are the reaction of 2,5-dialkylphenoxymagnesium bromides with cinnamaldehyde,[29] the reaction of resacetophenone with pyridine aldehydes,[30] and the pyridine-catalysed reaction of mesityl oxide with 4-hydroxycoumarin.[31]

[27] N. S. Narasimhan, M. V. Paradkar, and A. M. Gokhale, *Tetrahedron Letters*, 1970, 1665.

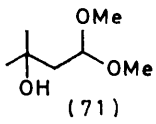
[28] *Inter alia*, E. M. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *J. Amer. Chem. Soc.*, 1966, **88**, 619; J. Kolc and R. S. Becker, *J. Phys. Chem.*, 1967, **71**, 4045; G. Cardillo, L. Merlini, and S. Servi, *Ann. Chim. (Italy)*, 1970, **60**, 564; R. Hug, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 10, 1675; A. Padwa and G. A. Lee, *J.C.S. Chem. Comm.*, 1972, 795.

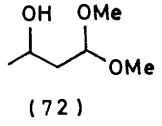
[29] G. Casiraghi, G. Casnati, and G. Salerno, *J. Chem. Soc.* (*C*), 1971, 2546.

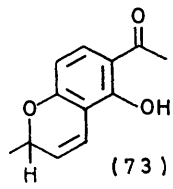
[30] K. Samula, *Roczniki Chem.*, 1971, **45**, 1833.

[31] D. W. Hutchinson and J. A. Tomlinson, *Tetrahedron Letters*, 1968, 5027.

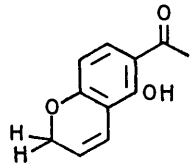
One was the expected chromen (74) (11%): the 3,4-location of the double bond is supported by the u.v.


(71)


(72)


(73)

spectrum which is very similar to that of the corresponding 2,2-dimethylchromen. The second product (28%) proved to be the ethyl acetal (75): n.m.r. data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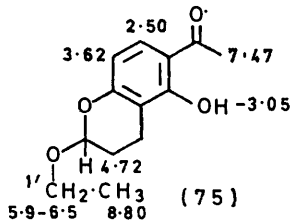
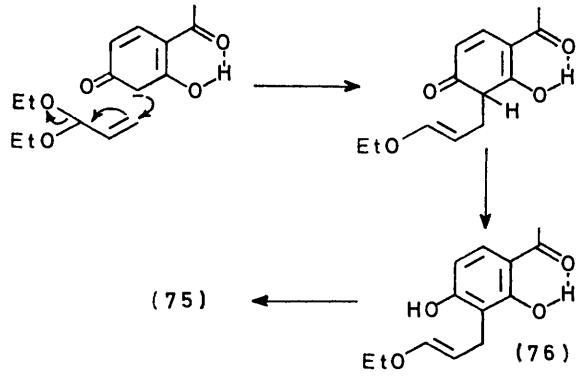

(75)

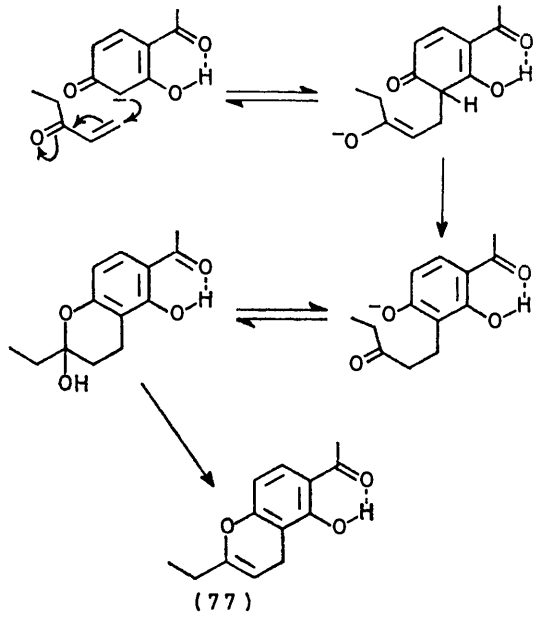
are shown and assignments were confirmed by spin-decoupling. Because of the C-2 dissymmetry, non-equivalent pairs of protons were observed at C-1′. The ethyl acetal is readily exchanged to give the methyl acetal in acidic methanol. The mechanism by which (75) is formed appears to involve S_N2' attack on the acetal (Scheme 3), a reaction suppressed, presumably for steric reasons, in the case of the acetals of crotonaldehyde and 3-methylcrotonaldehyde. Similar factors to those already discussed control the regiospecificity of attack in forming (75). The presumed intermediate (76) would


Scheme 3

be susceptible to acid-catalysed cyclisation, and this stage may be effected during isolation, *e.g.* chromatography on silica gel.

The possible use of unsaturated ketones in chromen formation was investigated by heating resacetophenone in pyridine with pulegone, mesityl oxide, or pent-3-en-2-one but no useful reaction was observed. However, ethyl vinyl ketone afforded the 4*H*-chromen (77) in low yield. This probably arises as in Scheme 4, by a mechanism involving *C*-Michael addition (contrast Scheme 2) permitted by lack of steric hindrance at the vinyl terminus.

Although our procedure for chromen formation has been used by us and others for synthesis of a variety of natural products,[1-9,15,26,27,32] in many cases little attempt has been made to optimise yields. Temperature, time, molar ratio of reagents, and possible catalysts are obvious variables, and a few experiments carried out with resacetophenone and citral in the presence of pyridine may be a useful guide. When equimolar ratios of the three reactants were used at 150°, the chromen (15; R^1 = Me, R^2 = $[CH_2]_2$·CH=CMe_2) was formed in *ca.* 70% yield after 12 h; the yield was not increased by further heating. At 100° the yield rose slowly over 4—5 days reaching 35—40%. When the proportion of citral was increased to 2 mol. equiv., the yield after 24 h at 100° was increased (from 25%) to 43%, but declined (25—30%) when more citral (3—5 mol. equiv.)


(77)

Scheme 4

was used. At 150°, after 24 h, the yield was reduced by adding an excess of citral (from 60—65% with 1—3 mol. equiv. to 40% with 4 mol. equiv.). There may be further reaction of the chromen with citral.

Increasing the molar ratio of pyridine above 2 mol. equiv. generally reduced the yield of chromen. At 150° a yield of 65% after 12 h obtained by using 1 mol. equiv. of pyridine was reduced to 8% with 13 mol. equiv. of pyridine. Substantial excesses of pyridine have been used in some condensations [26] and it has been reported that the ratio of linear to angular product in the formation of 2,2-dimethylchromens of 1,3-dihydroxy-5-methoxyxanthone is responsive to pyridine concentration.[32]

With a 1 : 1 : 1 molar mixture of citral, pyridine, and resacetophenone, the change in yield after 12 h at 150° as the pyridine ratio was reduced was studied. Constant volume was maintained by addition of solvent. No

[32] H. D. Locksley, A. J. Quillinan, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1971, 3804.

significant reduction in yield was noted with 0·5 mol. equiv. of pyridine and the appropriate volumes of dimethyl sulphoxide, decalin, or hexamethylphosphoramide. Even with 0·1 mol. equiv. of pyridine (12 h; 150°) reasonable yields were obtained, 40% with dimethyl sulphoxide as diluent, and 55% with decalin. This modification is useful for chromen formation from phenols insoluble in the pyridine–citral mixture.

Other bases catalyse the resacetophenone–citral reaction, including triethanolamine, *NN*-dimethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN),[33] and 1,8-bis-(dimethylamino)naphthalene,[34] but do not appear to have advantages over pyridine as a general reagent. The addition of benzoic acid (2%) to pyridine may lead to marginal improvement in yield (75%; 12 h) as has been reported.[27] On the other hand pyridine hydrochloride (5%) appeared to inhibit reaction (10% at 150°; 12 h) though it has been claimed to increase yields of chromen from phloroacetophenones.[15]

EXPERIMENTAL

Unless otherwise stated, the following generalisations apply. For t.l.c. 0·3 × 50 × 200 mm layers of silica gel G, developed with iodine vapour, were used. For preparative layer chromatography (p.l.c.) layers of silica gel G, or fluorescent gel (HF 254) were employed. Solvents were dried over magnesium sulphate and evaporated with a rotary evaporator. All analytical and spectroscopic data are deposited in Supplementary Publication No. SUP 20917 (9 pp.).*

Reactions of Phenols with Citral in Pyridine.—(a) *Resorcinol.* Resorcinol (3 g, 0·03 mol) was heated in pyridine (2·37 g, 0·03 mol) at 140°. Citral (9·12 g, 0·06 mol) was added dropwise during 30 min and heating was continued, with stirring, for 24 h. The pyridine was evaporated off and the residue was separated by p.l.c. (light petroleum–5% diethyl ether); two main bands were identified and eluted. The band of higher R_F afforded 2,8-*dimethyl*-2,8-*bis*-(4-*methylpent*-3-*enyl*)-2H,8H-*benzo*[1,2-b:3,4-b']*dipyran* (11) (95 mg, 1%); that of lower R_F gave the known linear benzodipyran (12) (450 mg, 4·7%).

(b) 3-*Hydroxyanisole.* 3-Hydroxyanisole (1·24 g, 0·01 mol) was heated in pyridine (0·79 g, 0·01 mol) at 120°. Citral (1·52 g, 0·01 mol) was added dropwise during 30 min, and heating was continued with stirring for 24 h. The cooled mixture was diluted with ether (25 cm³) and washed with dilute hydrochloric acid and aqueous sodium hydrogen carbonate. The ethereal solution was dried and evaporated, and the residue separated by p.l.c. (benzene). Two products were eluted from the main bands; the compound of higher R_F proved to be 7-*methoxy*-2-*methyl*-2-(4-*methylpent*-3-*enyl*)-2H-*chromen* (13) (85 mg, 3·3%), $n_D^{26·5}$ 1·5352; the second compound was the 5-*methoxy-isomer* (14) (159 mg, 6·2%), n_D^{22} 1·5460.

(c) 1-*Naphthol.* 1-Naphthol (1·44 g, 0·01 mol) was heated in pyridine (0·79 g, 0·01 mol) at 120°. Citral (1·52 g, 0·01 mol) was added dropwise during 30 min, and heating was continued with stirring for 20 h. The cooled mixture was dissolved in ether and washed with sodium hydroxide (2N), dilute hydrochloric acid, and aqueous sodium hydrogen carbonate. The dried ethereal solution was evaporated and the residual gum purified by chromatography on a silica gel column (150 g), with benzene as eluant. A pale yellow gum was obtained as the first fraction (250 mg, 9%), which was identified as 2-*methyl*-2-(4-*methylpent*-3-*enyl*)-2H-*naphtho*[1,2-b]*pyran* (48).

(d) 2-*Naphthol.* 2-Naphthol (1·44 g, 0·01 mol) was heated in pyridine (0·79 g, 0·01 mol) at 120°. Citral (1·52 g, 0·01 mol) was added dropwise during 30 min, and heating was continued, with stirring, for 20 h. The product, in ether, was washed with 2N-sodium hydroxide, dilute hydrochloric acid, and saturated aqueous sodium hydrogen carbonate; the solution was then dried and evaporated. The residual gum was chromatographed on a silica gel column (150 g). Elution with benzene afforded 3-*methyl*-3-(4-*methylpent*-3-*enyl*)-3H-*naphtho*[2,1-b]*pyran* (49) (200 mg, 7%).

(e) 2,3-*Dihydroxynaphthalene.* 2,3-Dihydroxynaphthalene (1·6 g, 0·01 mol) was heated in pyridine (0·79 g, 0·01 mol) at 160°, citral (1·52 g, 0·01 mol) was added during 30 min, and the reaction was continued, with stirring, for 18 h. The product was dissolved in ether and washed with dilute hydrochloric acid and aqueous sodium hydrogen carbonate. The solution was dried and evaporated. The residue was separated by p.l.c. (benzene–light petroleum 1 : 1) into two components. That of lower R_F was 5-*hydroxy*-3-*methyl*-3-(4-*methylpent*-3-*enyl*)-3H-*naphtho*[2,1-b]*pyran* (52) (1·05 g, 36%); the band of higher R_F afforded 2,11-*dimethyl*-2,11-*bis*-(4-*methylpent*-3-*enyl*)-2H,11H-*naphtho*[2,1-b:3,4-b']*dipyran* (78) (120 mg, 5·6%).

(f) 2,7-*Dihydroxynaphthalene.* 2,7-Dihydroxynaphthalene (0·01 mol) was treated as in (e). The products appeared very sensitive to air, decomposing to coloured materials. However one component was isolated by p.l.c. (benzene), and shown to be 9-*hydroxy*-3-*methyl*-3-(4-*methylpent*-3-*enyl*)-3H-*naphtho*[2,1-b]*pyran* (53) (577 mg, 19·6%).

(g) 2',6'-*Dihydroxyacetophenone.* 2',6'-Dihydroxyacetophenone (1·52 g, 0·01 mol) was heated in pyridine (0·79 g, 0·01 mol) at 120°. Citral (1·52 g, 0·01 mol) was added over 30 min, and the reaction was continued for 24 h. More citral (0·01 mol) was added after 6 h. Only one product was indicated by t.l.c. The mixture was diluted with chloroform, washed with dilute hydrochloric acid and aqueous sodium hydrogen carbonate, dried, and evaporated. The product was purified by chromatography on a silica gel column (150 g). 8-*Acetyl*-7-*hydroxy*-2-*methyl*-2-(4-*methylpent*-3-*enyl*)-2H-*chromen* (21) was eluted with benzene, and obtained as a pale orange gum (1 g, 35%).

(h) The following hydroxy-compounds were unchanged after heating with citral and pyridine (equimolar ratios) at 120° for 24 h and 160° for 96 h: 2',5'-dihydroxyacetophenone, *p*-hydroxyacetophenone, phenol, catechol, 4-nitrocatechol, purpurogallin, cyanuric acid, barbituric acid, quinoxaline-2,3-diol, 1,2-dihydroxynaphthalene, and 2-hydroxy-1,4-naphthoquinone.

Condensation of Resacetophenone with Acetals and Ketones.—(a) *Aldol dimethyl acetal.* Resacetophenone (1·52 g, 0·01 mol) was heated in pyridine (0·79 g, 0·01 mol) at 120°. Aldol dimethyl acetal (1·34 g, 0·01 mol) was added during 30 min, and heating was continued for 24 h. One product was indicated by t.l.c. The mixture was poured into ether, and washed with dilute hydrochloric acid and

* For details of Supplementary Publications see Notice to Authors No. 7 (*J.C.S. Perkin I*, 1972, Index Issue).

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aqueous sodium hydrogen carbonate. The dried ethereal solution was evaporated and the residue purified by p.l.c. to yield *6-acetyl-5-hydroxy-2-methyl-2H-chromen* (73) as a gum (160 mg, 8%).

(b) *Acrylaldehyde diethyl acetal.* Resacetophenone (1·52 g, 0·01 mol) was treated as in (a), but with acrylaldehyde diethyl acetal (1·3 g, 0·01 mol), for 20 h. Two products were shown by t.l.c. Evaporation of the pyridine left a brown residue, separated by p.l.c. (benzene). The main bands gave *6-acetyl-5-hydroxy-2H-chromen* (74) (200 mg, 11%) (higher R_F), and *6-acetyl-2-ethoxy-3,4-dihydro-5-hydroxy-2H-chromen* (75) (622 mg, 28%), m.p. 50—51° (lower R_F).

Treatment of the latter (100 mg) in refluxing methanol (2 cm³) with sulphuric acid (0·2 cm³) afforded the liquid *2-methoxy-analogue* (79) (86 mg, 91%).

(c) *Ethyl vinyl ketone.* Resacetophenone (0·01 mol) was treated as in (a), but with ethyl vinyl ketone (1·68 g, 0·02 mol) at 150°. The single product (t.l.c.), isolated by p.l.c. (benzene) after evaporation of the pyridine, proved to be *6-acetyl-2-ethyl-5-hydroxy-4H-chromen* (77) (109 mg, 5%).

Investigation of the Resacetophenone–Citral Reaction.— Resacetophenone (250 mg, 1·65 mmol) was dissolved in the required quantities of pyridine (150 mg, 1·65 mmol) and citral (250 mg, 1·65 mmol) and heated at the appropriate temperature. The mixture, in ethyl acetate (25 cm³) was extracted with N-sodium hydroxide (3 × 25 cm³), 2N-hydrochloric acid (1 × 25 cm³) and saturated aqueous sodium hydrogen carbonate (1 × 25 cm³). The dried extract was evaporated, and the residue dissolved in ethanol. The yield of chromen was assayed by u.v. spectroscopy (280—330 nm).

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