Novel Methods for the Synthesis of 2-2-Dimethylchromens

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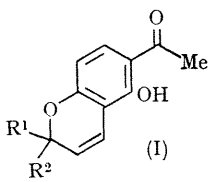
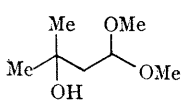
Summary 2,2-Dimethylchromens are synthesised by pyridine-catalysed condensation of 3-hydroxyisovaleraldehyde dimethyl acetal (or 3-methylcrotonaldehyde) with appropriate phenols, and, among other examples, the method is applied to lonchocarpin, evodionol 7-methyl ether, jacacreubin, and acronycine.

THE potential of the pyridine-catalysed condensation between citral and phenols[1] has been demonstrated by the synthesis of natural chromens (*e.g.* cannabichromene,[1–4]



(I)



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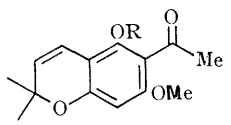

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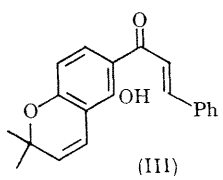
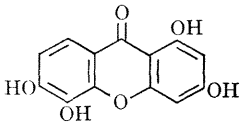


(III)

flemingin ethers,[5] *etc.*), tetracyclic phenol-bridged *p*-menthanes (*e.g.* deoxybruceol[1])† and tetracycles containing 1,2-fused four- and five-membered rings (*e.g.* cannabicyclol[2,6]). The reaction can be extended by the use of 3-methylcrotonaldehyde to give 2,2-dimethylchromens. A considerable variety of these types occur in Nature, but synthetic work has been hampered by deficiencies in earlier synthetic methods.[8] As an example of the present approach, 4-acetylresorcinol (1 mol.), heated (140°/12 hr.) with 3-methylcrotonaldehyde (4 mol.) and pyridine (1 mol.) gave the chromen (I; $R^1 = R^2 = Me$) (59%). This was converted into lonchocarpin (III)[9] (87%) by base-catalysed condensation with benzaldehyde.

We have now found that acetals may be used in place of aldehydes. For comparison of yields, 4-acetylresorcinol (1 mol.) and pyridine (1 mol.) were heated (150°/6 hr.) with citral (1 mol.) or its acetal (1 mol.). The chromen (I; $R^1 = CH_2{\cdot}CH_2{\cdot}CH:CMe_2$, $R^2 = Me$) was isolated in 84% yield from the aldehyde and 87% from the acetal. This has enabled us to replace the easily resinified 3-methylcrotonhyde by a stable and readily available reagent, 3-hydroxyisovaleraldehyde dimethyl acetal (II).[10] 4-Acetylresorcinol, heated (170—175°/12 hr.) with the latter (2 mol.) and

† The compound of this class formed from pinocembrin and citral, and reported in our previous communication[5] [formula (X) of the latter; the correctness of the orientation given has been confirmed by a study of the chromen intermediates], has since been shown to be identical with a new compound rubranine from *Aniba rosaeodora* Ducke.[7] We thank Dr. F. Winternitz for this information.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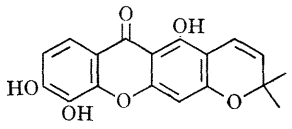
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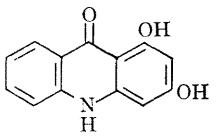
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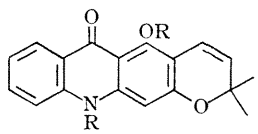
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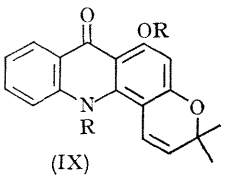
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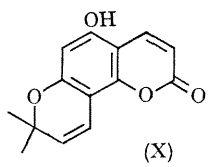
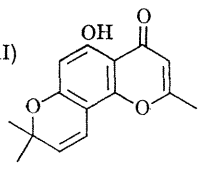

(X)


(XI)

pyridine (1 mol.), gave the chromen (I; $R^1 = R^2 = Me$) (53%). Similar condensation of the appropriate acetylphloroglucinol monomethyl ether with (II) (4 mol.) gave the chromen (IV; R = H) (68%) [orientations by n.m.r. acetate shifts method, Gibbs reaction, and other evidence]. Methylation gave the known[8,11] evodionol 7-methyl ether (IV; R = Me) (mixed m.p.).

When heated (160—165°/12 hr.) with (II) (4 mol.), and pyridine (2 mol.), the xanthone (V) gave jacareubin (VI) (20%) identical with natural material.[12] The acridone (VII), made by a one-step procedure,[13b] gave a mixture (32%) of linear (VIII; R = H) and angular (IX; R = H) products when condensed (150°/8 hr.) with (II) (3 mol.) and pyridine (3 mol.). On methylation, the mixture was readily separated to give acronycine (VIII; R = Me) (74%), identical with authentic material,[13] and isoacronycine (IX; R = Me) (25%). Acronycine is a promising anti-tumour agent from *Acronychia baueri*.[14]

Amongst other chromens prepared by the use of (II), 5,7-dihydroxycoumarin gave (X) (45%) and 2-methyl-5,7-dihydroxychromone gave (XI) (25%). Direct condensation of 4-acetylresorcinol with crotonaldehyde in the presence of pyridine gave (I; $R^1 = Me$, $R^2 = H$) (75%), but using cinnamaldehyde yields of (I; $R^1 = Ph$, $R^2 = H$) were poor (13%). Adjustment of reaction conditions sometimes effects substantial improvements in yield and those given are not necessarily optimal.

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