Selective Introduction of Mono-, Sesqui-, and Di-terpenoid Chromene Residues: Synthesis of Flemingin A, B, and C Methyl Ethers

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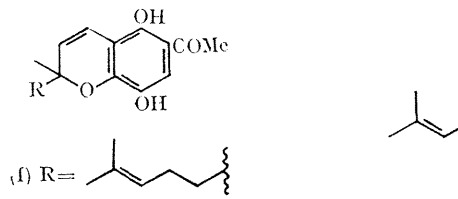
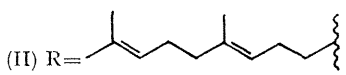
PYRIDINE-CATALYSED condensation of citral with resorcinols and phloroglucinols leads to chromenes, and other products having this oxidation level.[1] We now report that when one of two *ortho*-hydroxy-groups of the phenols is chelated, chromene ring formation specifically involves the other: further cyclisation to a tetracyclic system [*cf.* (X)] is inhibited and an excellent chromene synthesis results. Thus, reaction of citral with 2,4,5-trihydroxyacetophenone in refluxing pyridine (1 mol.) gave the monoterpenoid chromene (I) (60%) m.p. 87—89°.† Similarly farnesal gave the sesquiterpenoid (II) (42%) and phytal gave the diterpenoid (III) (39%).

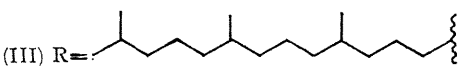


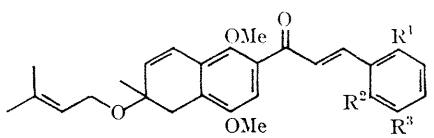
(I) R=

(II) R=



(III) R=

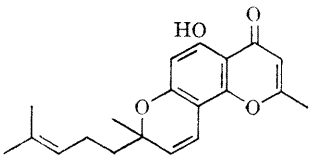




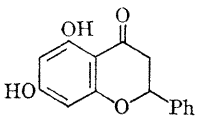
	R^1	R^2	R^3
(IV)	OH	H	H
(V)	OMe	H	H
(VI)	OMe	OMe	H
(VII)	OMe	H	OMe

† Cardillo *et al.*[2,3] have recently reported a synthesis of flemingin C trimethyl ether inwhich the chromene-forming step is alkenylation of 2,4-dihydroxy-5-methoxyacetophenone with geranyl bromide (%) followed by cyclodehydrogenation with 2,3-dichloro-5,6-dicyanoquinone (40%), *i.e. ca.* 3% overall. Other, existing methods for chromenes are also poor.

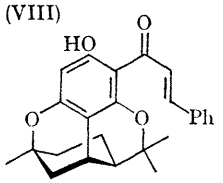
Condensation of the dimethyl ether of (I) with salicylaldehyde, salicylaldehyde methyl ether, 2,6-dimethoxybenzaldehyde, and 2,5-dimethoxybenzaldehyde under base catalysis gave respectively flemingin A di- and tri-methyl ethers (IV) and (V), flemingin B tetramethyl ether (VI), and flemingin C tetramethyl ether (VII). These are the methyl ethers of a group of natural products recently isolated from the drug "Wars".[3] After chromatographic purification, u.v., i.r., mass, and n.m.r. spectral data were in agreement with the suggested structures and with information from the parent phenols. All the ethers were oils, and this low crystallinity may be a reason why few such types have been isolated from natural sources.



(VIII)



(IX)



(X)

Reaction of citral with 5,7-dihydroxy-2-methylchromone gave the angularly-fused chromeno-chromone (VIII): none of the linearly-fused isomer was isolated. Citral and pinocembrin (IX) reacted in a similar way, but opening of the flavanone ring and further cyclisation ensued to give the tetracyclic chalcone (X) as the isolated product. [2-Cinnamoylation (X), as opposed to 5- appears more likely but has not been rigorously established.]

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[1] L. Crombie and R. Ponsford, *Chem. Comm.*, 168, 368, 894; *Tetrahedron Letters*, 1968, 4657.
[2] G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24**, 4825.
[3] G. Cardillo, L. Merlini, and R. Mondelli, *Tetrahedron*, 1968, **24**, 497.