Model Experiments in the Biosynthesis of Phenolic Isoprenoids

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IT has been suggested[1] that the biosynthesis of phenolic natural products, which contain isoprenoid residues, involves reaction between a phenol and 3,3-dimethylallyl pyrophosphate, and some biochemical evidence has been cited in support.[2] We now report chemical experiments which involve interaction of phenols and allyl or 3,3-dimethylallyl phosphate esters to give products analogous to those which occur naturally.

Thus phenol, when warmed in excess with allyl diphenyl phosphate (I; R = $CH_2 \cdot CH=CH_2$), gives a mixture of *p*-allylphenol and 2-methylcoumaran (II), together with traces of allyl phenyl ether. The coumaran (II) is formed by ring-closure of *o*-allylphenol, which is one of the initial products of the reaction. This cyclisation, which is catalysed by diphenyl hydrogen phosphate (I; R = H) formed in the reaction, can be prevented by addition of solid sodium hydrogen carbonate, so that *o*-allylphenol and *p*-allylphenol are the major products. When solid sodium phenoxide is heated with allyl diphenyl phosphate (I; R = $CH_2 \cdot CH=CH_2$) the only alkylated product is allyl phenyl ether.

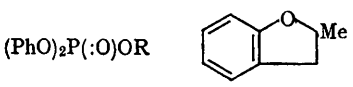
When phenol is warmed with 3,3-dimethylallyl diphenyl phosphate (I; R = $CH_2 \cdot CH=CMe_2$), 2,2-dimethylchroman (III; R = H) is formed. The corresponding *o*-(3,3-dimethylallyl)phenol could not be isolated when either sodium hydrogen carbonate or weak organic bases were added to the mixture before heating.

Quinol, when warmed with 3,3-dimethylallyl diphenyl phosphate (I; R = $CH_2 \cdot CH=CMe_2$) gives 6-hydroxy-2,2-dimethylchroman (III; R = OH), m.p. 74·5–75°, together with traces of a dichroman (IV or V), m.p. 157–158°.

Orcinol, under the same conditions, gives two monochromans, 5-hydroxy-2,2,7-trimethylchroman (VI; R = Me) and 7-hydroxy-2,2,5-trimethylchroman (VII; R = Me). The dichromans (VIII) and (IX) are also formed in this reaction. When heated with farnesyl diphenyl phosphate (I; R = farnesyl) orcinol yields two monochromans, one of which (VI; R = homogeranyl) has the same structure as that tentatively assigned[3] to the acid-catalysed rearrangement product of the antibiotic, grifolin (X).

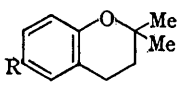
The structures of the products in all the above

[1] A. J. Birch, P. Eliot, and A. R. Penfold, *Austral. J. Chem.*, 1954, **7**, 169; A. J. Birch, *Fortschr. Chem. org. Naturstoffe*, 1957, **14**, 186; F. Lynen, *J. Cell. Comp. Physiol.*, 1959, **54**, *Suppl.* 1, 33.
[2] A. J. Birch, J. Schofield, and H. Smith, *Chem. and Ind.*, 1958, 1321.
[3] T. Goto, H. Kakisawa, and Y. Hirata, *Tetrahedron*, 1963, **19**, 2079.



(I)

(II)



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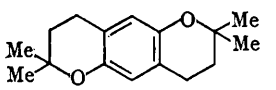

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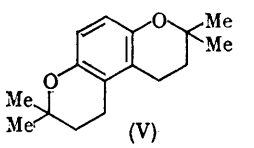

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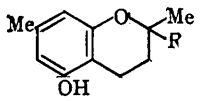

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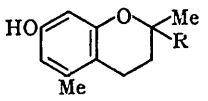

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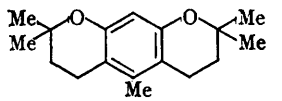

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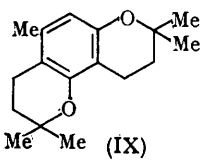

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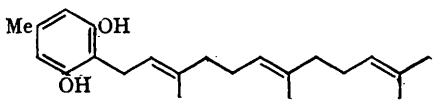

(X)

reactions were identified by spectroscopic methods and, when required, by microanalysis. The phosphate esters were synthesised by the conventional method from diphenyl phosphorochloridate and the appropriate alcohol in pyridine.[4]

These experiments establish that allylic phosphate esters can function as efficient alkylating agents in chemical systems. They also simulate the role played by pyrophosphate esters in biological systems and demonstrate the chemical feasibility of the biogenetic hypotheses which have been suggested.[1,5]

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[4] G. W. Kenner and J. Mather, *J.*, 1956, 3524.
[5] W. D. Ollis and I. O. Sutherland, "Chemistry of Natural Phenolic Compounds", Pergamon Press, Oxford, 1961, p. 74.